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Toxicological Profile for

ARSENIC

U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

TP-92/02

TOXICOLOGICAL PROFILE FOR ARSENIC

Prepared by:

Life Systems, Inc.
Under Subcontract to:

Clement International Corporation
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Prepared for:

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

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UPDATE STATEMENT

A Toxicological Profile for Arsenic was released in March 1989. This edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary, but no less than once every three years. For information regarding the update status of previously released profiles, contact ATSDR at:

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FOREWORD

The Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) extended and amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare toxicological profiles for hazardous substances which are most commonly found at facilities on the CERCLA National Priorities List and which pose the most significant potential threat to human health, as determined by ATSDR and the Environmental Protection Agency (EPA). The lists of the 250 most significant hazardous substances were published in the Federal Register on April 17, 1987, on October 20, 1988, on October 26, 1989, on October 17, 1990, and on October 17, 1991. A revised list of 275 substances was published on October 28, 1992.

Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the lists. Each profile must include the following:

(A) The examination, summary, and interpretation of available toxicological information and epidemiological evaluations on a hazardous substance in order to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects.

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure which present a significant risk to human health of acute, subacute, and chronic health effects.

(C) Where appropriate, identification of toxicological testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

This toxicological profile is prepared in accordance with guidelines developed by ATSDR and EPA. The original guidelines were published in the Federal Register on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile is intended to characterize succinctly the toxicological and adverse health effects information for the hazardous substance being described. Each profile identifies and reviews the key literature (that has been peer-reviewed) that describes a hazardous substance's toxicological properties. Other pertinent literature is also presented but described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

Each toxicological profile begins with a public health statement, which describes in nontechnical language a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health will be identified by ATSDR and EPA. The focus of the profiles is on health and toxicological information; therefore, we have included this information in the beginning of the document.

Foreword

The principal audiences for the toxicological profiles are health professionals at the federal, state, and local levels, interested private sector organizations and groups, and members of the public.

This profile reflects our assessment of all relevant toxicological testing and information that has been peer reviewed. It has been reviewed by scientists from ATSDR, the Centers for Disease Control and Prevention (CDC), and other federal agencies. It has also been reviewed by a panel of nongovernment peer reviewers and is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Green Border Review. Green Border review assures the consistency with ATSDR policy.

2. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying endpoints.

3. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific minimal risk levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.

4. Quality Assurance Review. The Quality Assurance Branch assures that consistency across profiles is maintained, identifies any significant problems in format or content, and establishes that Guidance has been followed.

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1. PUBLIC HEALTH STATEMENT

This Statement was prepared to give you information about arsenic and to emphasize the human health effects that may result from exposure to it. The Environmental Protection Agency (EPA) has identified 1,300 sites on its National Priorities List (NPL). Arsenic has been found in at least 781 of these sites. However, we do not know how many of the 1,300 NPL sites have been evaluated for arsenic. As EPA evaluates more sites, the number of sites at which arsenic is found may change. This information is important for you to know because arsenic may cause harmful health effects and because these sites are potential or actual sources of human exposure to arsenic.

When a chemical is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment as a chemical emission. This emission, which is also called a release, does not always lead to exposure. You can be exposed to a chemical only when you come into contact with the chemical. You may be exposed to it in the environment by breathing, eating, or drinking substances containing the chemical or from skin contact with it.

If you are exposed to a hazardous chemical such as arsenic, several factors will determine whether harmful health effects will occur and what the type and severity of those health effects will be. These factors include the dose (how much), the duration (how long), the route or pathway by which you are exposed (breathing, eating, drinking, or skin contact), the other chemicals to which you are exposed, and your individual characteristics such as age, sex, nutritional status, family traits, life style, and state of health.

1.1 WHAT IS ARSENIC?

Arsenic is a naturally-occurring element. Pure arsenic is a gray metal-like material which is usually found in the environment combined with other elements such as oxygen, chlorine, and sulfur. Arsenic combined with these elements is called inorganic arsenic. Arsenic combined with carbon and hydrogen is called organic arsenic. You should know the difference between inorganic and organic arsenic because the organic forms are usually less harmful than the inorganic forms.

Most inorganic and organic arsenic compounds are white or colorless powders that do not evaporate. They have no smell, and most have no special taste. Thus, you usually cannot tell if arsenic is present in your food, water, or air.

Inorganic arsenic occurs naturally in many kinds of rock, especially in ores that contain copper or lead. When these ores are heated at smelters to get the copper or lead, most of the arsenic enters the air as a fine dust. Smelters collect this dust and purify the arsenic for several uses. The main use is as a preservative for wood to make it resistant to rotting and

decay. Arsenic is also used to make several types of insect killers and weed killers, such as Ansar®, Scorch®, Phytar®, Bueno®, Crab-E-Rad®, Premix®, and others.

You can find more information on the sources, properties, and uses of arsenic in Chapters 3 and 4.

1.2 WHAT HAPPENS TO ARSENIC WHEN IT ENTERS THE ENVIRONMENT?

Arsenic can enter the environment in several ways. Even though it does not evaporate, arsenic can get into air as dust. This can happen when smelters heat ores containing arsenic, when people burn any material containing arsenic, or when wind blows soil that contains arsenic into the air. Once in the air, the arsenic particles will travel with the wind for a while, but will then settle back to the ground. Most arsenic compounds can also dissolve in water. Thus, arsenic can get into lakes, rivers, or underground water by dissolving in rain or snow, or through the discharge of industrial wastes. Some of the arsenic will stick to the sediment on the bottom of the lake or river, and some will be carried along by the water.

Arsenic is not broken down or destroyed in the environment. However, it can change from one form to another by natural chemical reactions, and also by the action of bacteria that live in soil or water. Although some fish and shellfish build up arsenic in their tissues, most of this is in a form (often called "fish arsenic") that is not toxic.

You can find more information on how arsenic gets into the environment and how it behaves in air, soil, and water in Chapters 4 and 5.

1.3 HOW MIGHT I BE EXPOSED TO ARSENIC?

Because arsenic is a natural part of the environment, low levels of arsenic are present in soil, water, food, and air. Soil usually contains the most, with average levels of about 5,000 parts of arsenic per billion parts of soil (ppb). Levels in food are usually about 20–140 ppb and levels in water are about 2 ppb. Levels in air are usually about 0.02–0.10 micrograms per cubic meter. Thus, you normally take in small amounts of arsenic in the air you breathe, the water you drink, and the food you eat. Of these, food is usually the largest source. You are also likely to swallow small amounts of dust or dirt each day, so this is another way you can be exposed to arsenic. The total amount you take in from these sources is probably about 50 micrograms each day.

In addition to the normal levels of arsenic in air, water, soil, and food, you could be exposed to higher levels in several ways, such as the following:

- Some areas of the country contain unusually high natural levels of arsenic in rock, and this can lead to unusually high levels of arsenic in soil or water. If you live in an area like this, you could take in above-average amounts of arsenic from the soil or from the water.

- Some hazardous waste sites contain large quantities of arsenic. If the material is not properly disposed of, it can get into surrounding water, air, or soil. If you live near such a site, you could be exposed to above-average levels of arsenic from these media.

- If you work in an occupation that involves arsenic production or use (for example, copper or lead smelting, wood treating, pesticide application), you could be exposed to above-average levels of arsenic during your work. The government estimates that about 55,000 people may be exposed in this way.

- If you saw or sand arsenic-treated wood, you could inhale some of the sawdust into your nose or throat. Similarly, if you burn arsenic-treated wood, you could inhale arsenic in the smoke.

- In the past, several kinds of products used in the home (rat poison, ant poison, weed killer, some types of medicines) had arsenic in them. However, most of these uses of arsenic have ended, so you are not likely to be exposed from home products any longer.

You can find more information on how you may be exposed to arsenic in Chapter 5.

1.4 HOW CAN ARSENIC ENTER AND LEAVE MY BODY?

If you swallow arsenic in water, soil, or food, most of the arsenic quickly enters into your body. This is the most likely way for you to be exposed near a waste site. If you breathe air that contains arsenic dusts, many of the dust particles settle onto the lining of the lungs. Most of the arsenic in these particles is then taken up from the lungs into the body. You might be exposed in this way near waste sites where arsenic-contaminated soils are allowed to blow into the air. If you get arsenic-contaminated soil or water on your skin, only a small amount will go through your skin into your body, so this is usually not of concern.

If you are exposed to arsenic, your liver changes some of this to a less harmful organic form. Both inorganic and organic forms leave your body in your urine. Most of the arsenic will be gone within several days, although some will remain in your body for several months or even longer.

You can find more information on how arsenic enters and leaves your body in Chapter 2.

1.5 HOW CAN ARSENIC AFFECT MY HEALTH?

Inorganic arsenic has been recognized as a human poison since ancient times, and large oral doses (above 60,000 ppb in food or water) can produce death. If you swallow lower levels of inorganic arsenic (ranging from about 300 to 30,000 ppb in food or water), you may experience irritation of your stomach and intestines, with symptoms such as pain, nausea, vomiting, and diarrhea. Other effects you might experience from swallowing arsenic include decreased production of red and white blood cells, abnormal heart rhythm, blood-vessel damage, and impaired nerve function causing a "pins and needles" sensation in your hands and feet. Although there is no good evidence that arsenic can injure pregnant women or their fetuses, studies in animals show that doses of arsenic that are large enough to cause illness in pregnant females may cause low birth weight, fetal malformations, or even fetal death.

Perhaps the single most characteristic effect of long-term oral exposure to inorganic arsenic is a pattern of skin changes. This includes a darkening of the skin and the appearance of small "corns" or "warts" on the palms, soles, and torso. While these skin changes are not considered to be a health concern in their own right, a small number of the corns may ultimately develop into skin cancer. Swallowing arsenic has also been reported to increase the risk of cancer in the liver, bladder, kidney, and lung. The Department of Health and Human Services determined that arsenic is a known carcinogen. The International Agency for Research on Cancer (IARC) has determined that arsenic is carcinogenic to humans. The EPA has determined that arsenic is a human carcinogen. Both the EPA and the National Toxicology Program (NTP) have classified arsenic as a known human carcinogen.

If you breathe high levels of inorganic arsenic, you are likely to experience a sore throat and irritated lungs. You may also develop some of the skin effects mentioned above. The exposure level that produces these effects is uncertain, but is probably above 100 micrograms per cubic meter. However, these effects are usually not serious. Of much greater concern is the ability of inhaled inorganic arsenic to increase the risk of lung cancer. This has been seen mostly in humans exposed to arsenic in or around smelters. People who live near smelters, chemical factories, or waste sites with arsenic may have increased risk of lung cancer as well.

If you have direct skin contact with inorganic arsenic compounds, your skin may become irritated with some redness and swelling. However, it does not appear that skin contact is likely to lead to any serious internal effects.

Despite all the adverse health effects associated with inorganic arsenic exposure, there is some evidence that the small amounts of arsenic in the normal diet (10–50 ppb) may be beneficial to your health. For example, animals fed a diet with unusually low concentrations of arsenic did not gain weight normally. They also became pregnant less frequently than animals fed a diet containing a normal amount of arsenic. Further, the offspring from these animals tended to be smaller than normal, and some died at an early age. However, no cases of arsenic deficiency in humans have ever been reported.

Almost no information is available on the effects of organic arsenic compounds in humans. Studies in animals show that most organic arsenic compounds are less toxic than the inorganic forms. However, high doses can produce some of the same effects. Thus, if you are exposed to high doses of an organic arsenic compound, you might develop nerve injury, stomach irritation, or other effects, but this is not known for certain.

You can find more information on the health effects of inorganic and organic arsenic in Chapter 2.

1.6 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO ARSENIC?

Several sensitive and specific tests can measure arsenic in your blood, urine, hair, or fingernails, and these tests are often helpful in determining if you have been exposed to above-average levels of arsenic. These tests are not usually performed in a doctor's office, but require sending the sample to a testing laboratory.

Measurement of arsenic in your urine is the most reliable means of detecting arsenic exposures that you experienced within the last several days. Most tests measure the total amount of arsenic present in your urine. Sometimes this can be misleading, because the nonharmful forms of arsenic in fish and shellfish can give a high reading even if you have not been exposed to a toxic form of arsenic. For this reason, laboratories sometimes use a more complicated test to separate "fish arsenic" from other forms. Because most arsenic leaves your body within a few days, analysis of your urine cannot detect if you were exposed to arsenic in the past. Tests of your hair or fingernails can tell if you were exposed to high levels over the past 6–12 months, but these tests are not very useful in detecting low level exposures. If high levels of arsenic are detected, this shows that you have been exposed, but unless more is known about when you were exposed and for how long, it is usually not possible to predict whether you will have any harmful health effects.

You can find more information on how arsenic can be measured in your hair, urine, nails, and other tissues in Chapters 2 and 6.

1.7 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government has taken several steps to protect humans from arsenic. First, EPA has set limits on the amount of arsenic that industrial sources can release into the environment. Second, EPA has restricted or canceled many of the uses of arsenic in pesticides and is considering further restrictions. Third, EPA has set a limit of 50 ppb for arsenic in drinking water. EPA is currently reviewing this value and may lower it. Finally, the Occupational Safety and Health Administration (OSHA) has established a maximum permissible exposure limit of 10 micrograms per cubic meter for airborne arsenic in various workplaces that use inorganic arsenic.

You can find more information on regulations and guidelines that apply to arsenic in Chapter 7.

1.8 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department or:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE, E-29
Atlanta, Georgia 30333

This agency can also provide you with information on the location of the nearest occupational and environmental health clinic. These clinics specialize in the recognition, evaluation, and treatment of illnesses resulting from exposure to hazardous substances.

2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective of the toxicology of arsenic and a depiction of significant exposure levels associated with various adverse health effects. It contains descriptions and evaluations of studies and presents levels of significant exposure for arsenic based on toxicological studies and epidemiological investigations.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure--inhalation, oral, and dermal--and then by health effect--death, systemic, immunological, neurological, developmental, reproductive, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods--acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. These distinctions are intended to help the users of the document identify the levels of exposure at which adverse health effects start to appear. They should also help to determine whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the tables and figures may differ depending on the user's perspective. For example, physicians concerned with the interpretation of clinical findings in exposed persons may be interested in levels of exposure associated with "serious" effects. Public health officials and project managers concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAEL) or exposure levels below which no adverse effects (NOAEL) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels, MRLs) may be of interest to health professionals and citizens alike.

Levels of exposure associated with the carcinogenic effects of arsenic are indicated in Figures 2-1 and 2-3. Because cancer effects could occur at lower exposure levels, the figures also show a range for the upper bound of estimated excess risks, ranging from a risk of 1 in 10,000 to 1 in 10,000,000 (10^{-4} to 10^{-7}), as developed by EPA.

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made, where data were believed reliable, for the most sensitive noncancer effect for each exposure duration. MRLs include adjustments to reflect human variability and extrapolation of data from laboratory animals to humans.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1989b), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

Chemical Forms of Concern

Analysis of the toxic effects of arsenic is complicated by the fact that arsenic can exist in several different valence states and many different inorganic and organic compounds. Most cases of human toxicity from arsenic have been associated with exposure to inorganic arsenic, so these compounds are the main focus of this profile.

The most common inorganic arsenical in air is arsenic trioxide (As_2O_3), while a variety of inorganic arsenates (AsO_4^{-3}) or arsenites (AsO_2^-) occur in water, soil, or food. A number of studies have noted differences in the relative toxicity of these compounds, with trivalent arsenites tending to be somewhat more toxic than pentavalent arsenates (Byron et al. 1967; Gaines 1960; Maitani et al. 1987a; Sardana et al. 1981; Willhite 1981). However, these distinctions have not been emphasized in this profile, for several reasons: (1) in most cases, the differences in the relative potency are reasonably small (about 2–3 fold), often within the bounds of uncertainty regarding NOAEL or LOAEL levels; (2) different forms of arsenic may be interconverted, both in the environment (see Section 5.3) and the body (see Section 2.3); and (3) in many cases of human exposure (especially those involving intake from water or soil, which are of greatest concern to residents near wastes sites), the precise chemical speciation is not known. Thus, for the purposes of simplicity and practicability, it is convenient to consider the arsenates and arsenites as approximately equitoxic.

Gallium arsenide (GaAs) is another inorganic arsenic compound of potential human health concern, due to its widespread use in the microelectronics industry. Available toxicokinetic data suggest that although gallium arsenide is poorly soluble, it undergoes slow dissolution and oxidation to form gallium trioxide and arsenite (Webb et al. 1984, 1986). Therefore, the toxic effects of this compound are expected to be attributable to the arsenite that is liberated, plus the additional effects of the gallium species.

It is beyond the scope of this profile to provide detailed toxicity data on other less common inorganic arsenic compounds (e.g., As_2S_3), but these are expected to be of approximately equal or lesser toxicity than the oxycompounds, depending mainly on solubility (see Section 2.3).

Although organic arsenicals are usually viewed as being less toxic than the inorganics, several methyl and phenyl derivatives of arsenic that are widely used in agriculture are of possible human health concern. Chief among these are monomethyl arsonic acid (MMA) and its salts (monosodium methane arsonate [MSMA] and disodium methane arsonate [DSMA]), dimethyl arsinic acid (DMA, also known as cacodylic acid) and its sodium salt (sodium dimethyl arsinite, or sodium cacodylate), and roxarsone (3-nitro-4-hydroxyphenylarsonic acid). As with the inorganic compounds, there are toxicological differences between these various organic derivatives, but for the purposes of this profile these differences have not been emphasized. This is because data are rarely adequate to permit rigorous quantitative comparisons between different chemicals, and most data are derived from studies in animals. As discussed below, animals do not appear to be good quantitative models for inorganic arsenic toxicity in humans, but it is not known if this also applies to toxicity of organic arsenicals.

Several organic arsenicals are found to accumulate in fish and shellfish. These derivatives (mainly arsenobetaine and arsenocholine, also referred to as "fish arsenic") have been studied by several researchers and have been found to be essentially nontoxic (Brown et al. 1990; Cannon et al. 1983; Charbonneau et al. 1978a; Kaise et al. 1985; Luten et al. 1982; Siewicki 1981; Tam et al. 1982; Yamauchi et al. 1986a). Thus, these compounds are not considered further here.

Arsine (AsH_3) and its methyl derivatives, although highly toxic, are also not considered in this profile, since these compounds are either gases or volatile liquids that are unlikely to be present at levels of concern at hazardous waste sites.

Use of Animal Data

An additional complexity to the analysis of arsenic toxicity is that most laboratory animals appear to be substantially less susceptible to arsenic than humans. For example, chronic oral exposure of humans to inorganic arsenic at doses of 0.05–0.1 mg/kg/day is frequently associated with neurological or hematological signs of arsenic toxicity, but no characteristic neurological or hematological signs of arsenism were detected in monkeys, dogs, or rats chronically exposed to arsenate or arsenite at doses of 0.7–2.8 mg As/kg/day (Byron et al. 1967; Heywood and Sortwell 1979; Schaumburg 1980). Moreover, while there is good evidence that arsenic is carcinogenic in humans by both the oral and inhalation routes, evidence of arsenic-induced carcinogenicity in animals is mostly negative. For these reasons, quantitative dose-response data from animals are not judged to be reliable for determining levels of significant human exposure, and will be considered only briefly except when human data are lacking.

2.2.1 Inhalation Exposure

Most information on human inhalation exposure to arsenic derives from occupational settings such as smelters and chemical plants, where the predominant form of airborne arsenic is arsenic trioxide dust. One limitation to this type of study is that exposure data are usually difficult to obtain, especially from earlier time periods when exposure levels were higher than in recent years. This is further complicated by the fact that significant oral and dermal exposures are also likely to occur under these conditions and that exposure to other metals and chemicals is also common. Thus, studies of this type are, like all epidemiological studies, subject to some limitations and uncertainties. Table 2-1 and Figure 2-1 summarize studies which provide the most reliable quantitative data on health effects in humans, along with several studies in animals exposed to arsenic trioxide and other inorganic arsenic compounds by the inhalation route. Data for organic arsenicals are shown in Table 2-2 and Figure 2-2. All exposure data are expressed as milligrams of arsenic (as the element) per cubic meter of air (mg As/m^3). These studies and others that provide useful qualitative information on health effects of inorganic and organic arsenicals are discussed below.

2.2.1.1 Death

Inorganic Arsenicals

Although there are many studies of humans exposed to arsenic in air, no cases of lethality from short-term exposure were located. This suggests that death is not likely to be of concern, even at the very high exposure levels (1–100 mg As/m^3) that used to be encountered in the workplace (e.g., Enterline and Marsh 1982; Jarup et al. 1989; Lee-Feldstein 1986). Delayed lethality attributable to increased risk of cardiovascular disease or lung cancer is discussed below in Sections 2.2.1.2 and 2.2.1.8, respectively. No studies were located regarding lethality in animals after inhalation exposure to inorganic arsenicals.

Organic Arsenicals

No studies were located regarding death in humans after inhalation exposure to organic arsenicals. As shown in Table 2-2 and Figure 2-2, the LC_{50} value for DMA in female rats is 2,100 mg As/m^3 (Stevens et al. 1979). Male rats and mice appear to be less susceptible, with only a few deaths at exposures of 3,470–3,700 mg As/m^3 (Stevens et al. 1979). The cause of death was not specified, but was probably due to lung injury (see Section 2.2.1.2). These values are so high that it is appropriate to conclude that there is no significant risk of acute lethality from the concentrations of DMA that might be encountered in the environment or the workplace.

TABLE 2-1. Levels of Significant Exposure to Inorganic Arsenic - Inhalation

Key to figure[a]	Species	Exposure duration/ frequency	System	NOAEL (mg As/m³)	LOAEL (effect) Less serious (mg As/m³)	LOAEL (effect) Serious (mg As/m³)	Reference	Valence
ACUTE EXPOSURE								
Immunological								
1	Mouse	1 d 3hr/d			0.94 (injury to alveolar macrophages)		Aranyi et al. 1985	As(+3)
Developmental								
2	Mouse	4 d Gd9-12 4hr/d		2		20 (29% fetal deaths, 62% skeletal malformations)	Nagymajtenyi et al. 1985	As(+3)
INTERMEDIATE EXPOSURE								
Systemic								
3	Human	2 mo (occup)	Hemato Hepatic Resp Renal	0.11 0.11 0.11 0.11			Ide and Bullough 1988	As(+3)
Immunological								
4	Mouse	4 wk 5d/wk 3hr/d		0.25	0.5 (injury to alveolar macrophages)		Aranyi et al. 1985	As(+3)
Neurological								
5	Human	2 mo (occup)			0.11 (nausea, anorexia)		Ide and Bullough 1988	As(+3)

TABLE 2-1. Levels of Significant Exposure to Inorganic Arsenic - Inhalation *(continued)*

Key to figure[a]	Species	Exposure duration/ frequency	System	NOAEL (mg As/m³)	LOAEL (effect) Less serious (mg As/m³)	LOAEL (effect) Serious (mg As/m³)	Reference	Valence
CHRONIC EXPOSURE								
Systemic								
6	Human	2-50 yr (occup)	Resp Derm/oc	1.0	0.078 (hyperpigmentation in 16/40, warts in 2/40)		Perry et al. 1948	ND
7	Human	23 yr (occup)	Cardio			0.5 (Raynauds disease in 10/46)	Lagerkvist et al. 1986	As(+3)
8	Human	14-40 yr (occup)	Cardio			0.05 (Raynauds disease)	Lagerkvist et al. 1988	As(+3)
Cancer								
9	Human	1+ yr (occup)				0.03 CEL (lung cancer; SMR = 183)	Lee-Feldstein 1986	As(+3)
10	Human	13-22 yr (occup)				0.3 CEL (lung cancer; SMR = 303)	Welch et al. 1982	As(+3)
11	Human	1-30 yr (occup)				0.055 CEL (lung cancer; SMR = 206)	Enterline et al. 1987a	As(+3)
12	Human	3-22 yr (occup)				0.07 CEL (lung cancer; SMR = 227)	Enterline et al. 1987b	As(+3)
13	Human	1-30 yr (occup)				0.01 CEL (lung cancer; SMR = 270)	Jarup et al. 1989	As(+3)

[a]The number corresponds to entries in Figure 2-1.

Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Derm/oc = dermal/ocular; Gastro = gastrointestinal; Gd = gestational days; Hemato = hematological; hr = hour(s); LOAEL = lowest-observed-adverse-effect level; mo = month(s); ND = no data; NOAEL = no-observed-adverse-effect level; occup = occupational; Resp = respiratory; SMR = standardized mortality ratio; wk = week(s); x = time(s); yr = year(s)

FIGURE 2-1. Levels of Significant Exposure to Inorganic Arsenic – Inhalation

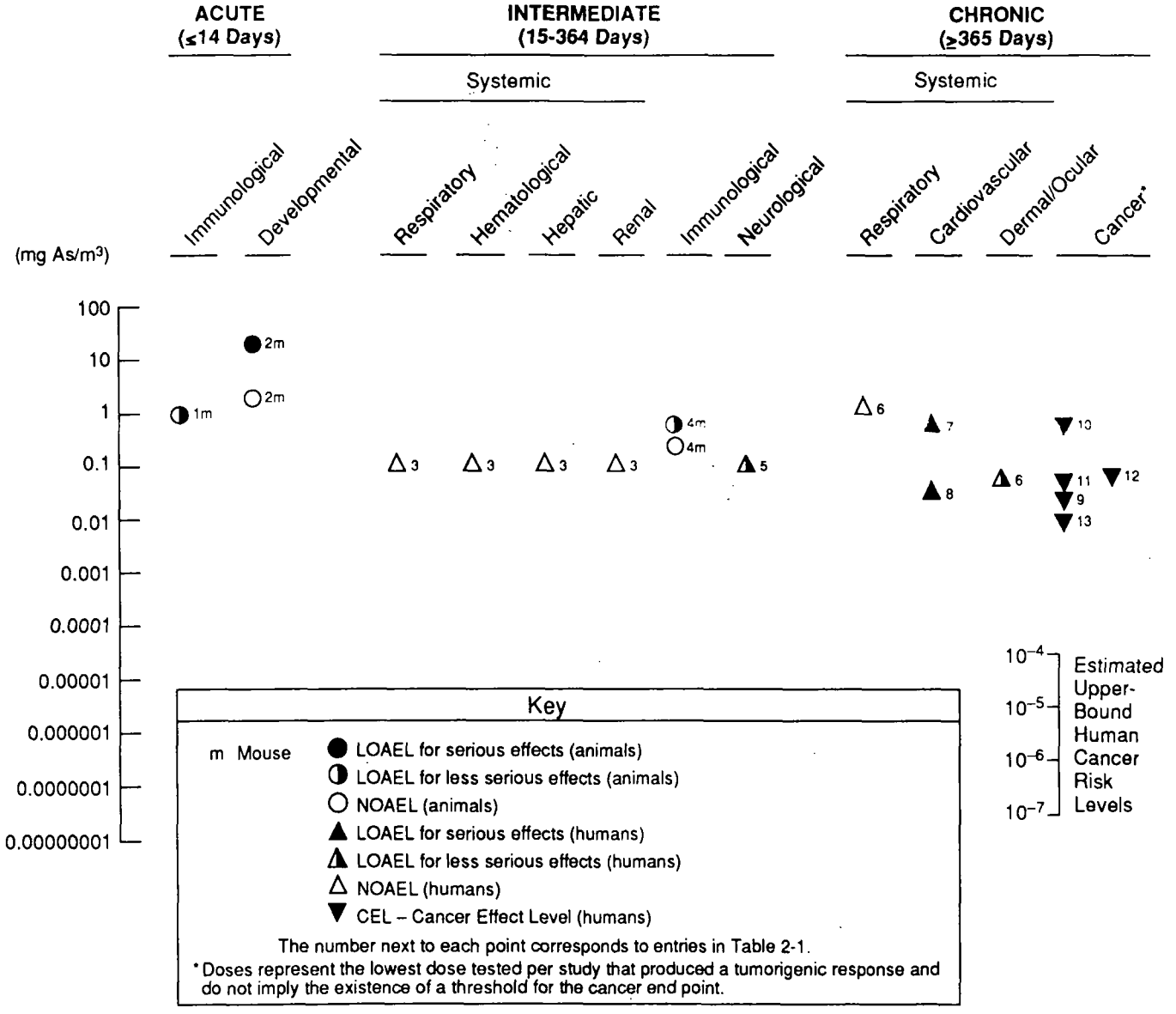


TABLE 2-2. Levels of Significant Exposure to Organic Arsenic - Inhalation

Key to figure[a]	Species	Exposure duration/ frequency	System	NOAEL (mg As/m³)	LOAEL (effect) Less serious (mg As/m³)	LOAEL (effect) Serious (mg As/m³)	Reference	Compound
ACUTE EXPOSURE								
Death								
1	Rat	2 hr				2100 (LC50 in females)	Stevens et al. 1979	DMA
2	Mouse	2 hr				3470 (death in 1/10 males)	Stevens et al. 1979	DMA
Systemic								
3	Rat	2 hr	Resp			2440 (respiratory distress)	Stevens et al. 1979	MMA
4	Rat	2 hr	Resp			2170 (respiratory distress)	Stevens et al. 1979	DMA
			Gastro		2170 (diarrhea)			
			Derm/oc		3770 (erythematous lesions on feet and ears)			
5	Mouse	2 hr	Resp			2170 (respiratory distress)	Stevens et al. 1979	DMA
			Gastro		2170 (diarrhea)			
6	Mouse	2 hr	Resp			2760 (respiratory distress)	Stevens et al. 1979	MMA

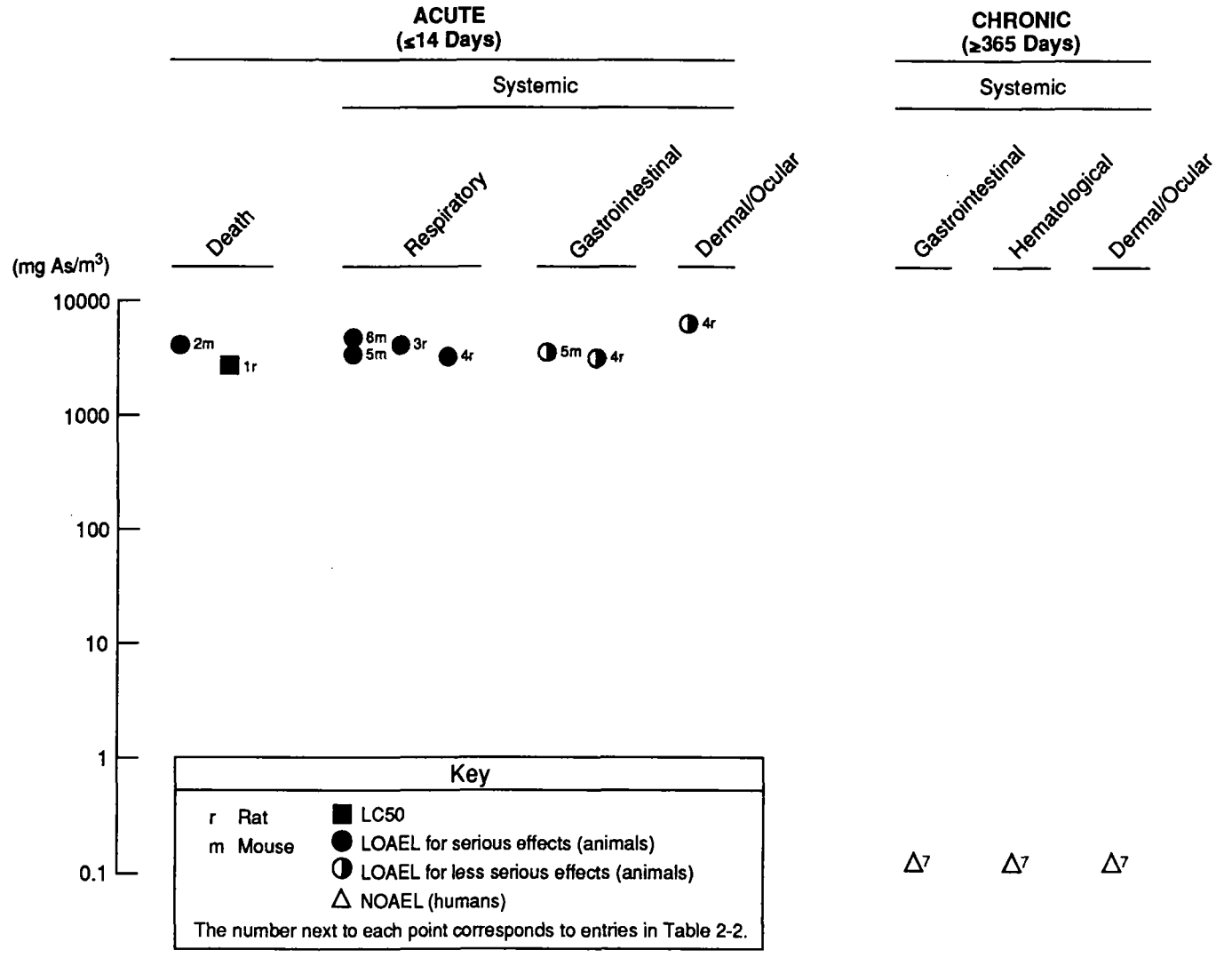
TABLE 2-2. Levels of Significant Exposure to Organic Arsenic - Inhalation *(continued)*

Key to figure[a]	Species	Exposure duration/ frequency	System	NOAEL (mg As/m^3)	LOAEL (effect) Less serious (mg As/m^3)	LOAEL (effect) Serious (mg As/m^3)	Reference	Compound
CHRONIC EXPOSURE								
Systemic								
7	Human	1-2 yr (occup)	Gastro Hemato Derm/oc	0.13 0.13 0.13			Watrous and McCaughey 1945	AA

[a]The number corresponds to entries in Figure 2-2.

AA = arsanilic acid; DMA = dimethylarsinic acid, or a corresponding salt (e.g., sodium dimethylarsinate); Derm/oc = dermal/ocular; Gastro = gastrointestinal; Hemato = hematological; hr = hour(s); LC50 = lethal concentration, 50% kill; LOAEL = lowest-observed-adverse-effect level; MMA = monomethylarsonic acid, or a corresponding salt (e.g., sodium methylarsonate or disodium methylarsonate); NOAEL = no-observed-adverse-effect level; occup = occupational; Resp = respiratory; yr = year(s)

Figure 2-2. Levels of Significant Exposure to Organic Arsenic – Inhalation



2.2.1.2 Systemic Effects

The highest NOAEL values and all reliable LOAEL values for systemic effects from inhalation exposure to inorganic arsenicals in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1, while the corresponding data for organic arsenicals are shown in Table 2-2 and Figure 2-2.

Respiratory Effects

Inorganic Arsenicals

Workers exposed to arsenic dusts in air often experience irritation to the mucous membranes of the nose and throat. This may lead to laryngitis, bronchitis, or rhinitis (Dunlap 1921; Morton and Caron 1989; Pinto and McGill 1953), and very high exposures (characteristic of workplace exposures in the past) can cause perforation of the nasal septum (Dunlap 1921; Pinto and McGill 1953). These effects (even the nasal perforation) were usually mild and did not cause impaired respiration (Perry et al. 1948) or require workers to take sick-leave (Pinto and McGill 1953). Insufficient data exist on the exposure levels in these studies to identify a no-effect level for respiratory tract irritation with confidence, but it appears such effects are minor or absent at exposure levels of about 0.1–1 mg/m^3 (Ide and Bullough 1988; Perry et al. 1948).

No studies were located regarding respiratory effects in animals after inhalation exposure to inorganic arsenicals, although intratracheal instillation of arsenic trioxide (13 mg As/kg) or gallium arsenide (1.5–52 mg As/kg) can cause marked irritation and hyperplasia of the lung of rats or hamsters (Goering et al. 1988; Ohyama et al. 1988; Webb et al. 1986, 1987). Since this sort of response is produced by a number of respirable particulate materials, it is likely that the inflammatory response is not specifically due to the arsenic.

Organic Arsenicals

No studies were located regarding respiratory effects in humans exposed to organic arsenicals. However, short-term exposure of rats and mice to high concentrations (2,170 mg As/m^3) of DMA caused respiratory distress, and necropsy of animals that died revealed bright red lungs with dark spots (Stevens et al. 1979). Similar results were observed in rats and mice exposed to high levels (2,440–2,760 mg As/m^3) of the disodium salt of MMA (Stevens et al. 1979). Since only high concentrations and brief exposures were used, it is not possible to conclude whether respiratory injury is of concern at the exposure levels and durations that may occur in the environment or the workplace.

Cardiovascular Effects

Inorganic Arsenicals

Several epidemiological studies of smelter workers suggest that chronic inhalation exposure to arsenic trioxide increases the risk of dying from cardiovascular disease (Axelson et al. 1978; Lee-Feldstein 1983; Wall 1980), although this is not observed in all studies (Jarup et al. 1989). Quantitative estimates of the exposure levels leading to this effect are not available, and other risk factors besides arsenic (e.g., lead, smoking) may also have contributed. Smelter workers exposed to arsenic trioxide dusts may also have an increased incidence of Raynaud's disease and an increased constriction of blood vessels in response to cold at exposure levels above about 0.05–0.5 mg As/m^3 (Lagerkvist et al. 1986, 1988). These findings indicate that long-term inhalation of inorganic arsenic may injure blood vessels and/or the heart. No studies were located regarding cardiovascular effects in animals after inhalation exposure to inorganic arsenic.

Organic Arsenicals

No studies were located regarding cardiovascular effects in humans or animals after inhalation exposure to organic arsenicals.

Gastrointestinal Effects

Inorganic Arsenicals

Several studies have reported the occurrence of nausea, vomiting, and diarrhea in workers exposed to high levels of arsenic dusts or fumes (Beckett et al. 1986; Bolla-Wilson and Bleecker 1987; Morton and Caron 1989). Most studies lack quantitative data on the exposure duration or exposure level that cause these effects, but Ide and Bullough (1988) reported nausea and anorexia in one worker (but not in another) exposed to arsenic trioxide at a concentration of about 0.11 mg As/m^3. These effects usually disappear if exposure ceases, and are rarely reported in workers exposed to lower levels of arsenic dust (Dunlap 1921; Pinto and McGill 1953). No studies were located regarding gastrointestinal effects in animals after inhalation exposure to inorganic arsenicals.

Organic Arsenicals

Workers exposed to low levels of arsanilic acid (an average of 0.13 mg As/m^3) in a chemical factory did not have an above-average incidence of gastrointestinal complaints to company doctors (Watrous and McCaughey 1945). However, this sort of data might easily be biased by workers who chose not to complain about minor symptoms, so no firm conclusion can be reached. Rats and mice exposed to very high levels (above 2,170 mg As/m^3) of DMA experienced diarrhea (Stevens et al. 1979). It seems likely that this might be due to transport of inhaled material from the lungs to the gastrointestinal system or to direct ingestion of the compound (e.g., from grooming of the fur), but this is not certain.

Hematological Effects

Inorganic Arsenicals

Although anemia is often noted in humans exposed to arsenic by the oral route (see Section 2.2.2.2), red blood cell counts are usually normal in workers exposed to inorganic arsenicals by inhalation (Beckett et al. 1986; Bolla-Wilson and Bleecker 1987; Ide and Bullough 1988; Morton and Caron 1989). The reason for this apparent route specificity is not clear, but might simply be related to dose. No studies were located regarding hematological effects in animals after inhalation exposure to inorganic arsenicals.

Organic Arsenicals

No effect on levels of red cells or white cells was detected in the blood of workers exposed to airborne arsanilic acid dusts (0.13 mg As/m^3) in the workplace (Watrous and McCaughey 1945). However, in the absence of data on other hematological end points and effects at other exposure levels, these data do not permit general conclusions about possible hematological effects of organic arsenicals. No studies were located regarding hematological effects in animals after inhalation exposure to organic arsenicals.

Musculoskeletal Effects

Inorganic Arsenicals

No studies were located regarding musculoskeletal effects in humans or animals after inhalation exposure to inorganic arsenicals.

Organic Arsenicals

No studies were located regarding musculoskeletal effects in humans or animals after inhalation exposure to organic arsenicals.

Hepatic Effects

Inorganic Arsenicals

Hepatic toxicity has not been thoroughly investigated in humans following inhalation exposure, but no evidence of hepatic dysfunction was detected by clinical examination of several workers exposed to arsenic dusts (Bolla-Wilson and Bleecker 1987; Ide and Bullough 1988). This suggests that liver injury is not likely to be of concern following inhalation exposure, but too few people have been studied to draw firm conclusions. No studies were located regarding hepatic effects in animals after inhalation exposure to inorganic arsenicals.

Organic Arsenicals

No studies were located regarding hepatic effects in humans or animals after inhalation exposure to organic arsenicals.

Renal Effects

Inorganic Arsenicals

Routine clinical urinalysis of workers exposed to arsenic dusts has not revealed evidence of kidney damage (Ide and Bullough 1988; Morton and Caron 1989). Similarly, no increases were detected in urinary levels of several proteins (albumin, retinol binding protein, β_2-microglobulin, brush-border antigen) that are indicators of glomerular damage or tubular cell exfoliation (Foa et al. 1987). These data indicate that the kidney is not likely to be injured by inhalation exposure to inorganic arsenicals. No studies were located regarding renal effects in animals after inhalation exposure to inorganic arsenicals.

Organic Arsenicals

No studies were located regarding renal effects in humans or animals after inhalation exposure to organic arsenicals.

Dermal/Ocular Effects

Inorganic Arsenicals

Dermal effects (hyperkeratoses, hyperpigmentation) are very common in people exposed to inorganic arsenic by the oral route (see Section 2.2.2.2), but similar effects are usually not mentioned in studies of persons exposed primarily by inhalation. However, Perry et al. (1948) did describe hyperpigmentation in 16/40 workers and warts (hyperkeratoses) in 2/40 workers chronically exposed at a concentration of about 0.078 mg As/m^3. The basis for this apparent route distinction is not clear, but could simply be related to dose. No studies were located on dermal or ocular effects in animals after inhalation exposure to inorganic arsenicals.

Organic Arsenicals

Workers exposed to low levels of arsanilic acid (average concentration = 0.13 mg As/m^3) for several years did not complain to doctors about dermal or ocular effects (Watrous and McCaughey 1945). However, as noted previously, workers might choose not to report minor complaints to company officials, so this observation is of uncertain significance. Rats exposed to high concentrations of DMA (3,770 mg As/m^3) developed erythematous lesions on the feet and ears, along with an encrustation around the eyes (Stevens et al. 1979). It seems likely these effects were due to direct irritation from dermal or ocular contact with the dust, but this is not certain.

2.2.1.3 Immunological Effects

Inorganic Arsenicals

Effects on the immune system following inhalation exposure to arsenic have not been well studied. No abnormalities in serum levels of immunoglobins could be detected in workers exposed to arsenic in a coal-burning power plant (Bencko et al. 1988), but the levels of arsenic were not measured, and may have been too low for this to be a meaningful result. In animals, single exposures of mice to arsenic trioxide (0.94 mg As/m^3) led to increased susceptibility to respiratory bacterial pathogens, apparently as a result of injury to alveolar macrophages (Aranyi et al. 1985). These findings are summarized in Table 2-1 and shown in Figure 2-1. A decreased humoral response to antigens and decreases in several complement proteins were noted in mice given an intratracheal dose of 5.7 mg As/kg as sodium arsenite (Sikorski et al. 1989), although these changes were not accompanied by any decrease in resistance to bacterial or tumor cell challenges. Animals given an intratracheal dose of GaAs (25 mg As/kg) also displayed a variety of changes in numerous immunological end points (some increased, some decreased) (Sikorski et al. 1989). Whether these effects were due to a direct effect on the immune system or were secondary to the inflammatory effect of GaAs on the lung (see Section 2.2.1.2, above) is uncertain. Overall, the results of the studies in animals suggest that inhalation of inorganic arsenicals can affect the immune system and may interfere with its function.

Organic Arsenicals

No studies were located regarding immunological effects in humans or animals after inhalation exposure to organic arsenicals.

2.2.1.4 Neurological Effects

Inorganic Arsenicals

Several case reports and epidemiological studies indicate that inhalation of inorganic arsenic can lead to neurological injury in humans. This may include both peripheral neuropathy of sensory and motor neurons (numbness, loss of reflexes, muscle weakness) (Feldman et al. 1979; Landau et al. 1977), as well as frank encephalopathy (hallucinations, agitation, emotional lability, memory loss) (Beckett et al. 1986; Morton and Caron 1989). The effects tend to diminish after exposure ceases (Bolla-Wilson and Bleecker 1987), but some effects may persist (Beckett et al. 1986). Available data are not sufficient to define a level of concern for the neurological effects of inhaled arsenic. No studies were located regarding neurological effects in animals after inhalation exposure to inorganic arsenicals.

Organic Arsenicals

No studies were located regarding neurological effects in humans or animals after inhalation exposure to organic arsenicals.

2.2.1.5 Developmental Effects

Inorganic Arsenicals

The developmental effects of airborne arsenic have been investigated in women who worked in a copper smelter in Sweden (Nordstrom et al. 1978a, 1979b). Babies born to women exposed to arsenic dusts during pregnancy had a higher-than expected incidence of congenital malformations (Nordstrom et al. 1979b), and average birth weight was slightly below average (Nordstrom et al. 1978a). Also, the incidence of spontaneous abortion in women who lived near the smelter tended to decrease as a function of distance from the smelter (Nordstrom et al. 1979a). These data are consistent with a possible developmental effect of arsenic, but no data were available to determine if there was a correlation between exposure and effect in the smelter, and a number of other chemicals (mainly lead, cadmium, and sulfur dioxide) were presumably also present. Thus, the role of arsenic in the etiology of these effects is difficult to judge.

As shown in Table 2-1 and Figure 2-1, exposure of mice to levels up to 2 mg As/m^3 (as As_2O_3) on days 9–12 of gestation produced only slight decreases in fetal weight, but higher levels of arsenic (20 mg As/m^3, as As_2O_3) produced a clear increase in skeletal malformations and an increase in fetal death (Nagymajtenyi et al. 1985). This shows that high levels of arsenic can cause developmental effects, but does not provide a basis for estimating a level of concern in humans.

Organic Arsenicals

No studies were located regarding developmental effects in humans or animals after inhalation exposure to organic arsenicals.

2.2.1.6 Reproductive Effects

Inorganic Arsenicals

No studies were located regarding reproductive effects in humans or animals after inhalation exposure to inorganic arsenicals.

Organic Arsenicals

No studies were located regarding reproductive effects in humans or animals after inhalation exposure to organic arsenicals.

2.2.1.7 Genotoxic Effects

Inorganic Arsenicals

Inhalation exposure to arsenic trioxide has been found to increase the frequency of chromosomal aberrations in peripheral lymphocytes of smelter workers (Beckman et al. 1977; Nordenson et al. 1978) and in livers of fetuses from mice exposed to 22 mg As/m^3 on days 9–12 of gestation (Nagymajtenyi et al. 1985). These data indicate that arsenic is clastogenic, but do not indicate whether it is mutagenic. Other genotoxicity studies on inorganic arsenicals are discussed in Section 2.4.

Organic Arsenicals

No studies were located regarding genotoxic effects in humans or animals after inhalation exposure to organic arsenicals. Other genotoxicity studies on organic arsenicals are discussed in Section 2.4.

2.2.1.8 Cancer

Inorganic Arsenicals

There is convincing evidence from a large number of epidemiological studies that inhalation exposure to inorganic arsenic increases the risk of lung cancer. Most studies have involved workers exposed primarily to arsenic trioxide dust in air at copper smelters (Axelson et al. 1978; Enterline and Marsh 1982; Enterline et al. 1987a, 1987b; Jarup et al. 1989; Lee-Feldstein 1983, 1986; Pinto et al. 1977, 1978; Wall 1980; Welch et al. 1982), but increased incidence of lung cancer has also been observed at chemical plants where exposure was primarily to arsenate (Mabuchi et al. 1979; Ott et al. 1974; Sobel et al. 1988). In addition, several studies suggest that residents living near smelters or arsenical chemical plants may also have increased risk of lung cancer (Brown et al. 1984; Cordier et al. 1983; Matanoski et al. 1981; Pershagen 1985), although the increases are small and are not clearly detectable in all cases (e.g., Frost et al. 1987).

Many of the studies provide only qualitative evidence for an association between duration and/or level of arsenic exposure and risk of lung cancer, but several studies provide sufficient exposure data to permit quantification of cancer risk. The calculations of exposure are quite complex in some cases, and the interested reader is referred to the EPA documents (EPA 1981, 1984a) for a detailed description. In general, the data indicate that there is an approximately linear increase in relative risk (the frequency of lung cancer in the exposed group divided by the frequency of lung cancer in the control group) as a function of increasing cumulative exposure (expressed as the product of average concentration of arsenic in air times the years of worker exposure at that

concentration). Based on the data, EPA (1984a) derived an overall unit risk estimate (the excess risk of lung cancer associated with lifetime exposure to 1 $\mu g/m^3$) of $4.3x10^{-3}$. Figure 2-1 shows the air concentrations that correspond to excess lifetime cancer risks of 10^{-4} to 10^{-7}. Figure 2-1 and Table 2-1 also present a number of estimated Cancer Effect Levels (CELs) for workers exposed to arsenic trioxide in air.

More recently, Enterline et al. (1987a) reexamined the dose-response relationship between inhalation exposure to arsenic and risk of lung cancer, using historical records of airborne arsenic levels in the smelters, along with records of urinary arsenic levels in exposed workers. These researchers concluded that arsenic is a more potent lung carcinogen than previously believed, with a dose-response relationship that becomes steeper at exposure levels below cumulative doses of 0.01 mg-yr/m^3.

Several researchers have examined the histological cell types of lung cancer (epidermoid carcinoma, small cell carcinoma, adenocarcinoma) in arsenic-exposed workers (e.g., Axelson et al. 1978; Newman et al. 1976; Pershagen et al. 1987; Wicks et al. 1981). Although the incidence of the various cell types varied from population to population, all studies found an increase in several tumor types. This indicates that arsenic does not specifically increase the incidence of one particular type of lung cancer.

No studies were located regarding cancer in animals after inhalation exposure to inorganic arsenicals, although several intratracheal instillation studies in hamsters have provided evidence that both arsenite and arsenate can increase the incidence of lung adenomas and/or carcinomas (Ishinishi et al. 1983; Pershagen and Bjorklund 1985; Pershagen et al. 1984a; Yamamoto et al. 1987). These data support the conclusion that inhalation of arsenic may lead to lung cancer in humans.

Organic Arsenicals

No studies were located regarding cancer effects in humans or animals after inhalation exposure to organic arsenicals.

2.2.2 Oral Exposure

There are a large number of studies in humans and animals on the toxic effects of ingested arsenic. In humans, most cases of toxicity have resulted from accidental, suicidal, homicidal, or medicinal ingestion of arsenic-containing powders or solutions, or by consumption of contaminated food or drinking water. In some cases the chemical form is known (e.g., the most common arsenic medicinal was Fowler's solution, which contained 1% potassium arsenite), but in many cases (e.g., exposures through drinking water), the chemical form is not known. In these cases, it is presumed the most likely forms are either inorganic arsenate (As+5), inorganic arsenite (As+3), or a mixture. Table 2-3 and Figure 2-3 summarize a number of studies which provide reliable quantitative data on health effects in humans and animals exposed to inorganic arsenicals by the oral route. Similar data for organic arsenicals are listed in Table 2-4 and shown in Figure 2-4. All exposure data are expressed as milligrams of arsenic (as the element) per kilogram body weight per day (mg As/kg/day). These studies and others that provide useful qualitative information are summarized below.

TABLE 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (mg As/kg/day)	LOAEL (effect) Less serious (mg As/kg/day)	LOAEL (effect) Serious (mg As/kg/day)	Reference	Valence
ACUTE EXPOSURE									
Death									
1	Human	(W)	ND 1 wk				2 (death of 2/8)	Armstrong et al. 1984	ND
2	Human	(ND)	1 d 1x/d				22 (suicide)	Levin-Scherz et al. 1987	As(+3)
3	Rat	(GW)	1 d 1x/d				39 (LD50)	Harrisson et al. 1958	As(+3)
4	Rat	(GW)	1 d 1x/d				44 (LD50)	Gaines 1960	As(+3)
5	Rat	(GW)	1 d 1x/d				15 (LD50)	Harrisson et al. 1958	As(+3)
6	Rat	(GW)	1 d 1x/d				110 (LD50)	Dieke and Richter 1946	As(+3)
7	Rat	(GW)	1 d 1x/d				110 (LD50)	Gaines 1960	As(+5)
8	Mouse	(GW)	1 d 1x/d				26 (LD50)	Kaise et al. 1985	As(+3)
Systemic									
9	Human	(W)	ND 1 wk	Gastro		1 (throat irritation, nausea, vomiting)		Armstrong et al. 1984	ND
				Hemato			1 (anemia, leukopenia)		
				Hepatic			1 (hepatitis, elevated serum transaminase levels)		
				Renal			1 (proteinuria, elevated serum creatine)		
10	Human	(ND)	1 d 1x/d	Resp			8 (hemorrhagic bronchitis)	Fincher and Koerker 1987	As(+3)
				Gastro			8 (gastrointestinal bleeding)		
				Hemato			8 (hemolysis)		
				Renal			8 (acute renal failure)		

TABLE 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral *(continued)*

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (mg As/kg/day)	LOAEL (effect) Less serious (mg As/kg/day)	LOAEL (effect) Serious (mg As/kg/day)	Reference	Valence
11	Monkey	(ML)	13 d	Gastro Hemato Renal	2.8 5.7 2.8	5.7 (vomiting, nausea) 5.7 (dilation of proximal tubules)		Heywood and Sortwell 1979	As(+5)
Neurological									
12	Human	(W)	ND 1 wk				1 (encephalopathy, peripheral neuropathy)	Armstrong et al. 1984	ND
13	Human	(ND)	1 d 1x/d				8 (encephalopathy)	Fincher and Koerker 1987	As(+3)
Developmental									
14	Mouse	(GW)	1 d 1x/d				68 (fetal malformations)	Hood et al. 1978	As(+3)
15	Mouse	(GW)	1 d 1x/d		11		23 (teratogenicity, fetal mortality)	Baxley et al. 1981	As(+3)
16	Hamster	(GW)	1 d 1x/d				14 (prenatal mortality)	Hood and Harrison 1982	As(+3)
INTERMEDIATE EXPOSURE									
Systemic									
17	Human	(F)	2-3 wk	Cardio		0.05 (abnormal electrocardiogram)		Mizuta et al. 1956	ND
				Gastro			0.05 (sore throat, nausea, anorexia, gastrointestinal bleeding)		
				Hemato		0.05 (mild anemia)			
				Hepatic		0.05 (mild hepatomegaly)			
				Renal	0.05				
				Resp	0.05				
				Derm/oc		0.05 (conjunctivitis, edema of eyelids)			

TABLE 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral *(continued)*

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (mg As/kg/day)	LOAEL (effect) Less serious (mg As/kg/day)	LOAEL (effect) Serious (mg As/kg/day)	Reference	Valence
18	Human	(W)	1-2 mo continuous	Hemato Gastro			0.29 (anemia, leukopenia) 0.29 (severe gastrointestinal irritation, diarrhea)	Franzblau and Lilis 1989	ND
				Derm/oc		0.29 (hyperkeratosis)			
19	Human	(FS)	several weeks	Gastro		0.08 (gastrointestinal pain, diarrhea)		Holland 1904	As(+3)
20	Human	(W)	4 mo	Gastro Derm/oc		0.06 (nausea, vomiting) 0.06 (hyperkeratosis)		Wagner et al. 1979	ND
21	Rat	(GW)	2-4 wk 5d/wk	Cardio	2.3	11 (decrease in vasoreactivity)		Bekemeier and Hirschelmann 1989	As(+3)
22	Rat	(W)	6 wk	Renal		4.7 (increased organ weight, impaired mitochondrial respiration)		Brown et al. 1976	As(+5)
23	Dog	(F)	183 d	Hepatic	4.6			Neiger and Osweiler 1989	As(+3)
Immunological									
24	Mouse	(W)	10-12 wk		20			Kerkvliet et al. 1980	As(+5)
Neurological									
25	Human	(W)	1-2 mo continuous				0.29 (paresthesia of hands and feet)	Franzblau and Lilis 1989	ND
26	Human	(F)	2-3 wk			0.05 (hypesthesia in legs)		Mizuta et al. 1956	ND
27	Human	(W)	4 mo				0.06 (weakness, paresthesia)	Wagner et al. 1979	ND
Reproductive									
28	Mouse	(W)	3 gen continuous		1.0			Schroeder and Mitchener 1971	As(+3)

TABLE 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral *(continued)*

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (mg As/kg/day)	LOAEL (effect) Less serious (mg As/kg/day)	LOAEL (effect) Serious (mg As/kg/day)	Reference	Valence
CHRONIC EXPOSURE									
Death									
29	Dog	(F)	2 yr				3.1 (death in 6/6 given As+3, death in 1/6 given	Byron et al. 1967	As(+3) AS(+5)
30	Monkey	(ML)	1 yr				2.8 (2/7 died)	Heywood and Sortwell 1979	As(+5)
Systemic									
31	Human	(W)	continuous	Cardio			0.014 (Blackfoot disease)	Tseng 1989	ND
32	Human	(W)	1-11 yr continuous	Hepatic Derm/oc		0.019 (hepatomegaly) 0.019 (melanosis, keratosis)		Chakraborty and Saha 1987	ND
33	Human	(W)	15 yr	Derm/oc		0.06 (hyperpigmentation, keratoses in children)		Zaldivar 1977	ND
34	Human	(FS)	55 yr	Hepatic			0.03 (portal fibrosis and hypertension, bleeding from esophageal varices)	Szuler et al. 1979	As(+3)
				Derm/oc		0.03 (hyperkeratosis)			
35	Human	(W)	ND residential	Hemato Derm/oc	0.0009 0.0009			Southwick et al. 1981	ND
36	Human	(W)	45 yr residential	Cardio			0.014 (Blackfoot disease)	Tseng 1977	ND
37	Human	(W)	45 yr residential	Derm/oc	0.0008[b]	0.014 (hyperkeratosis and hyperpigmentation)		Tseng et al. 1968	ND
38	Human	(FS)	15 yr	Hepatic Derm/oc		0.05 (hyperkeratosis)	0.05 (central fibrosis)	Piontek et al. 1989	As(+3)

TABLE 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral *(continued)*

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (mg As/kg/day)	LOAEL (effect) Less serious (mg As/kg/day)	LOAEL (effect) Serious (mg As/kg/day)	Reference	Valence
39	Human	(FS)	2-6 yr	Hepatic			0.08 (cirrhosis, ascites)	Franklin et al. 1950	As(+3)
				Derm/oc		0.08 (hyperpigmentation, hyperkeratosis)			
40	Human	(FS)	4 yr	Derm/oc		0.1 (hyperkeratosis)		Bickley and Papa 1989	As(+3)
41	Human	(W)	10 yr residential	Gastro Hemato Derm/oc	0.003 0.003 0.003			Harrington et al. 1978	ND
42	Human	(W)	12 yr	Cardio			0.02 (arterial thickening in 5 children)	Rosenberg 1974	ND
43	Human	(FS)	2-3 yr	Hemato	0.072			Silver and Wainman 1952	As(+3)
				Hepatic		0.072 (hepatomegaly, fatty liver)			
				Renal	0.072				
				Derm/oc		0.072 (hyperkeratosis, hyperpigmentation)			
				Gastro		0.072 (nausea, cramps)			
44	Human	(W)	continuous	Gastro		0.03 (abdominal pain)		Mazumder et al. 1988	ND
				Hepatic		0.03 (hepatomegaly)			
				Derm/oc	0.0009	0.03 (pigmentation changes, hyperkeratosis)			
45	Human	(W)	0.5-15 yr	Gastro		0.05 (abdominal pain)		Huang et al. 1985	ND
				Hemato	0.05				
				Hepatic	0.05				
				Derm/oc		0.05 (pigmentation changes, hyperkeratosis)			
46	Human	(W)	continuous	Gastro	0.0004	0.022 (gastrointestinal irritation)		Cebrian et al. 1983	As(+5)
				Derm/oc	0.0004	0.022 (pigmentation changes, hyperkeratosis)			
47	Human	(FS)	16 mo	Hepatic		0.1 (hepatomegaly)		Wade and Frazer 1953	As(+3)
				Derm/oc		0.1 (hyperpigmentation, hyperkeratosis)			

TABLE 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral *(continued)*

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (mg As/kg/day)	LOAEL (effect) Less serious (mg As/kg/day)	LOAEL (effect) Serious (mg As/kg/day)	Reference	Valence
48	Human	(W)	1-39 yr	Cardio			0.06 (arterial thickening, Raynaud's disease)	Zaldivar and Guillier 1977	ND
49	Human	(W)	12 yr	Cardio			0.02 (Raynaud's disease)	Borgono and Greiber 1972	ND
				Gastro		0.02 (diarrhea, abdominal pain)			
				Derm/oc		0.02 (abnormal pigmentation)			
50	Human	(FS)	3-22 yr	Hepatic			0.05 (vascular fibrosis, portal hypertension)	Morris et al. 1974	As(+3)
51	Human	(W)	11-15 yr]	Derm/oc		0.01 (hypo- and hyperpigmentation hyperkeratosis)		Borgono et al. 1980	ND
52	Human	(W)	12 yr	Cardio			0.017 (Raynaud's disease, thrombosis)	Zaldivar 1974	ND
				Derm/oc		0.017 (abnormal pigmentation, hyperkeratosis)			
53	Human	(W)	contin-uous	Cardio			0.02 (Blackfoot disease)	Chen et al. 1988b	ND
54	Human	(W)	ND resi-dential	Gastro	0.01			Valentine et al. 1985	ND
				Derm/oc	0.01				
55	Rat	(F)	2 yr	Resp	12			Byron et al. 1967	As(+3) AS(+5)
				Cardio	12				
				Gastro	12				
				Hemato	12				
				Hepatic	3.2	6.4 (enlargement of the bile duct)			
				Renal	12				
56	Rat	(W)	2 yr	Cardio	0.7			Schroeder et al. 1968	As(+3)
				Hemato	0.7				
57	Rat	(F)	1 yr	Hemato	20			Kroes et al. 1974	As(+5)

TABLE 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral *(continued)*

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (mg As/kg/day)	LOAEL (effect) Less serious (mg As/kg/day)	LOAEL (effect) Serious (mg As/kg/day)	Reference	Valence
58	Dog	(F)	2 yr	Resp Cardio Gastro Hemato Hepatic Renal	1.2 1.2 1.2 1.2 1.2 1.2			Byron et al. 1967	As(+3) As(+5)
Neurological									
59	Human	(W)	contin-uous		0.0007	0.019 (electromyographic abnormalities)	0.04 (functional denervation)	Hindmarsh et al. 1977	ND
60	Human	(W)	ND residen-tial		0.006			Southwick et al. 1981	ND
61	Human	(W)	10 yr residen-tial		0.003			Harrington et al. 1978	ND
62	Human	(W)	ND resi-dential		0.01			Valentine et al. 1985	ND
63	Human	(FS)	2-3 yr				0.072 (paresthesia)	Silver and Wainman 1952	As(+3)
64	Human	(W)	0.5-15 yr				0.05 (mild peripheral neuropathy)	Huang et al. 1985	ND
65	Dog	(F)	2 yr		3.1			Byron et al. 1967	As(+3) As(+5)
66	Monkey	(ML)	1 yr		2.8			Heywood and Sortwell 1979	As(+5)
Cancer									
67	Human	(W)	45 yr residen-tial				0.014 CEL (squamous cell carcinoma of the skin)	Tseng et al. 1968	ND
68	Human	(W)	14-23 yr contin-uous				0.009 CEL (basal cell and squamous cell carcinomas of the skin)	Zaldivar et al. 1981	ND

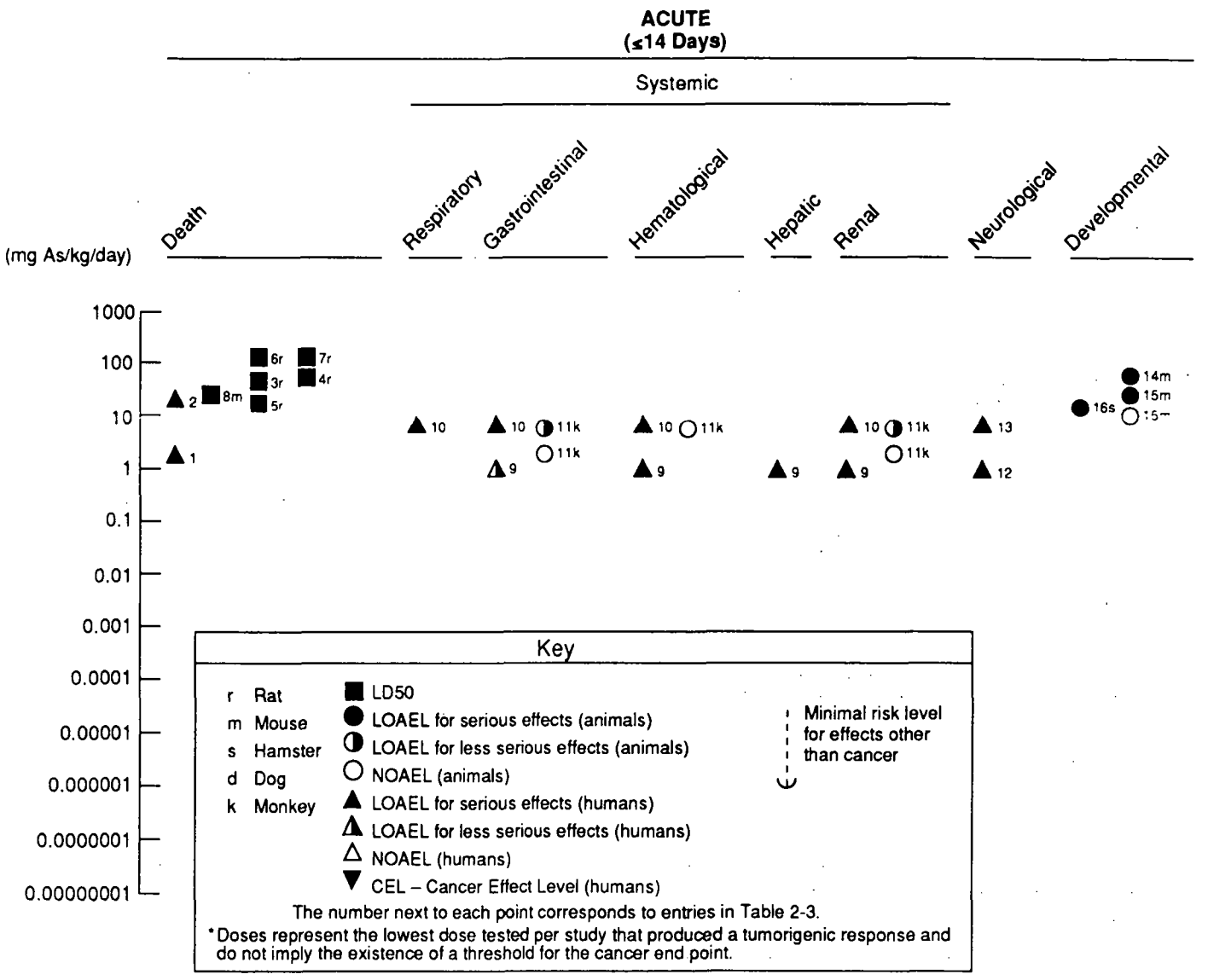
TABLE 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral *(continued)*

Key to figure[a]	Species	Route	Exposure duration/ frequency	NOAEL System (mg As/kg/day)	LOAEL (effect) Less serious (mg As/kg/day)	LOAEL (effect) Serious (mg As/kg/day)	Reference	Valence
69	Human	(W)	12 yr			0.017 CEL (squamous cell carcinoma of the skin)	Zaldivar 1974	ND
70	Human	(FS)	15 yr			0.03 CEL (hepatic angiosarcoma)	Lander et al. 1975	As(+3)
71	Human	(W)	contin-uous			0.02 CEL (malignant neoplasms of the bladder, skin, lung and liver)	Chen et al. 1988b	ND
72	Human	(W)	contin-uous			0.02 CEL (bladder, lung, liver)	Chen et al. 1986	ND
73	Human	(WN)	16 yr (ave occup)			0.04 CEL (basal cell and squamous cell carcinomas of the skin, small cell and squamous cell carcinoma of the lung)	Luchtrath 1983	As(+5)
74	Human	(W)	60 yr contin-uous			0.038 CEL (intraepidermal carcinoma)	Tseng 1977	ND

[a]The number corresponds to entries in Figure 2-3.
[b]Used to derive a chronic oral Minimal Risk Level (MRL) of 0.0003 mg/kg/day; dose divided by an uncertainty factor of 3 for human variability.

As = arsenic; avg = average; (C) = capsule; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Derm/oc = dermal/ocular; (F) = feed; (FS) = Fowlers' solution; Gastro = gastrointestinal; gen = generation; (GW) = gavage water; Hemato = hematological; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; (ML) = milk; mo = month(s); ND = no data; NOAEL = no-observed-adverse-effect level; Resp = respiratory; SMR = standardized mortality ratio; (W) = water; wk = week(s); WN = wine; x = time(s); yr = year(s)

FIGURE 2-3. Levels of Significant Exposure to Inorganic Arsenic – Oral



The number next to each point corresponds to entries in Table 2-3.

*Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer end point.

FIGURE 2-3. Levels of Significant Exposure to Inorganic Arsenic – Oral (Continued)

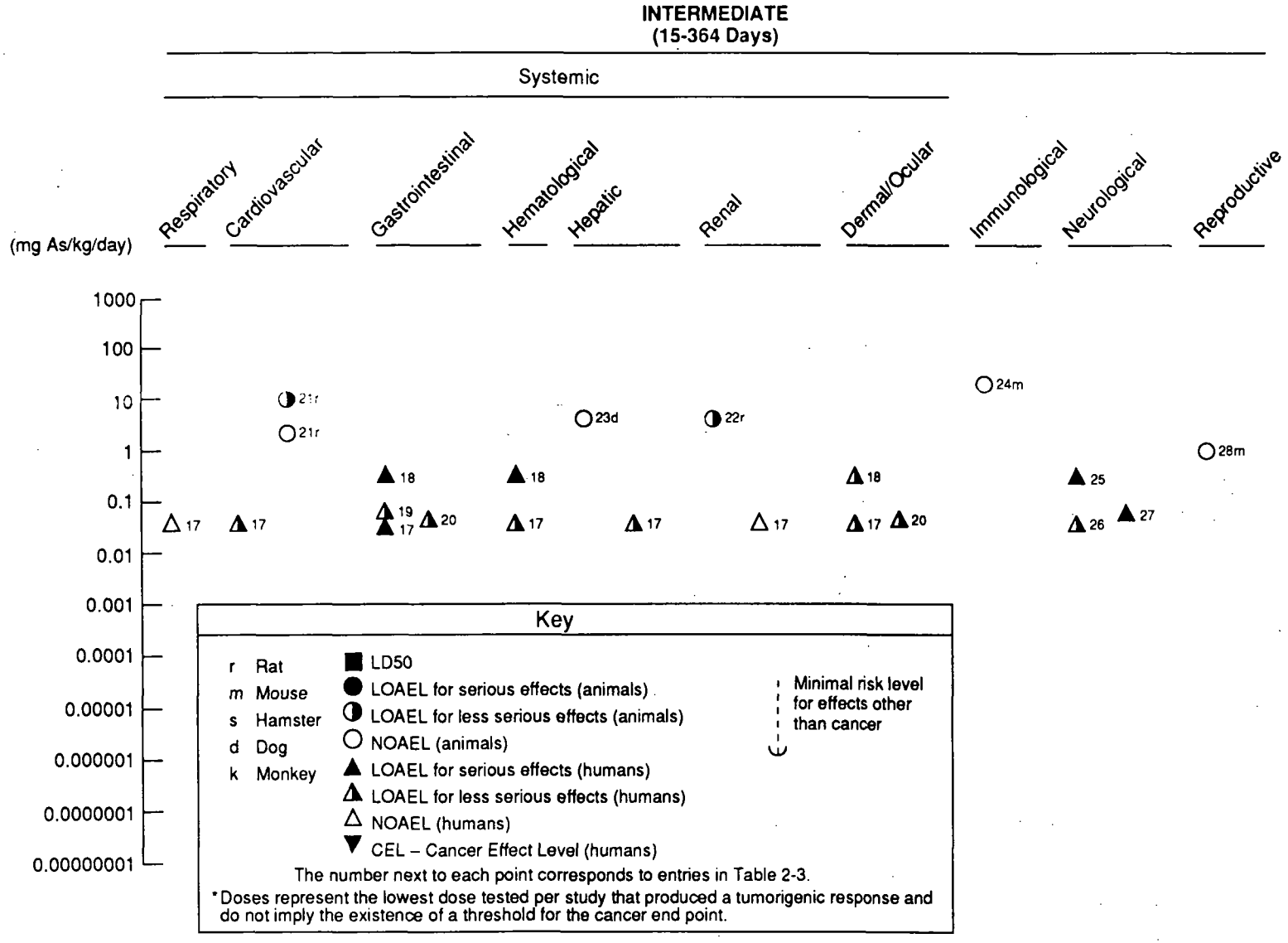


FIGURE 2-3. Levels of Significant Exposure to Inorganic Arsenic – Oral (Continued)

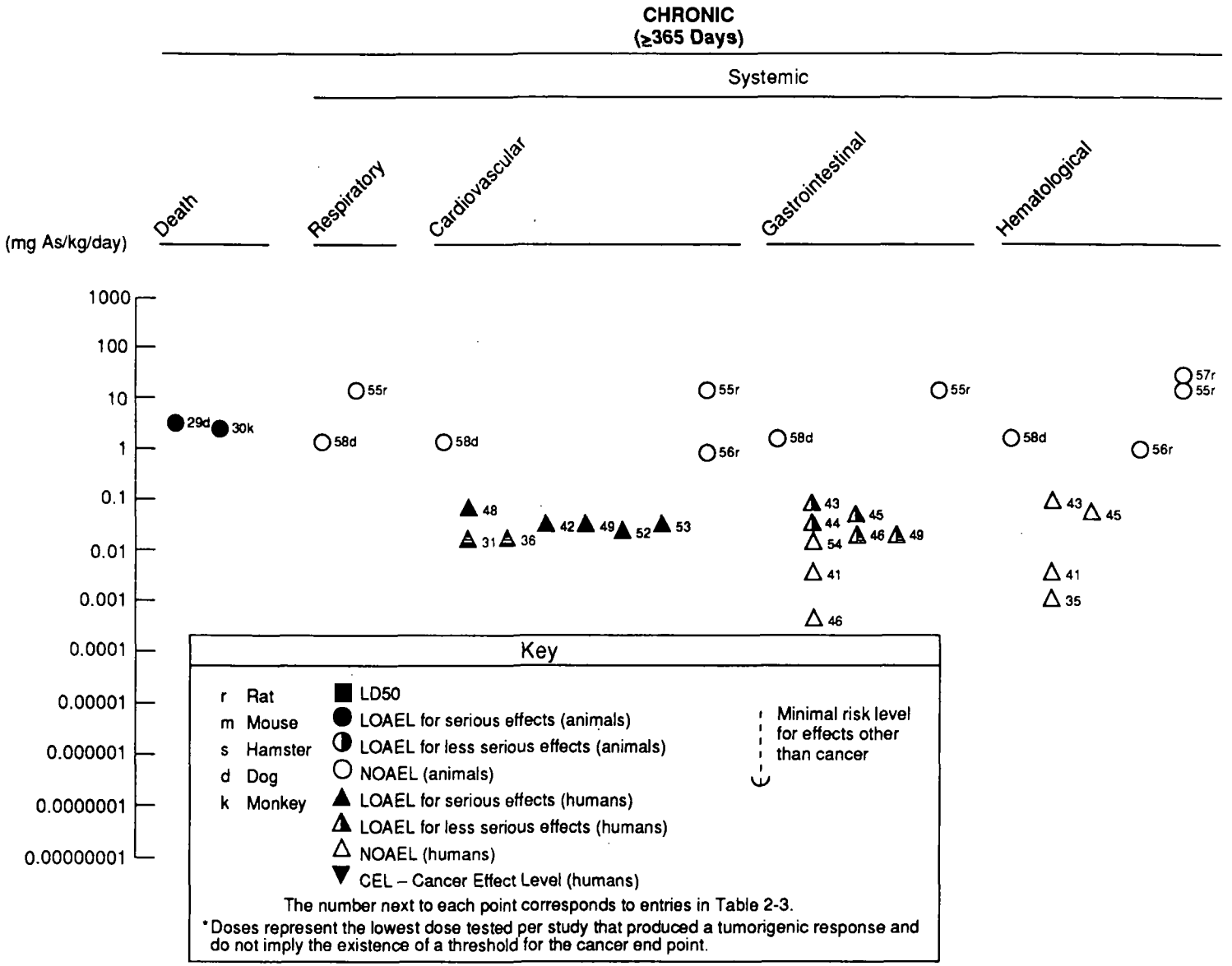


FIGURE 2-3. Levels of Significant Exposure to Inorganic Arsenic – Oral (Continued)

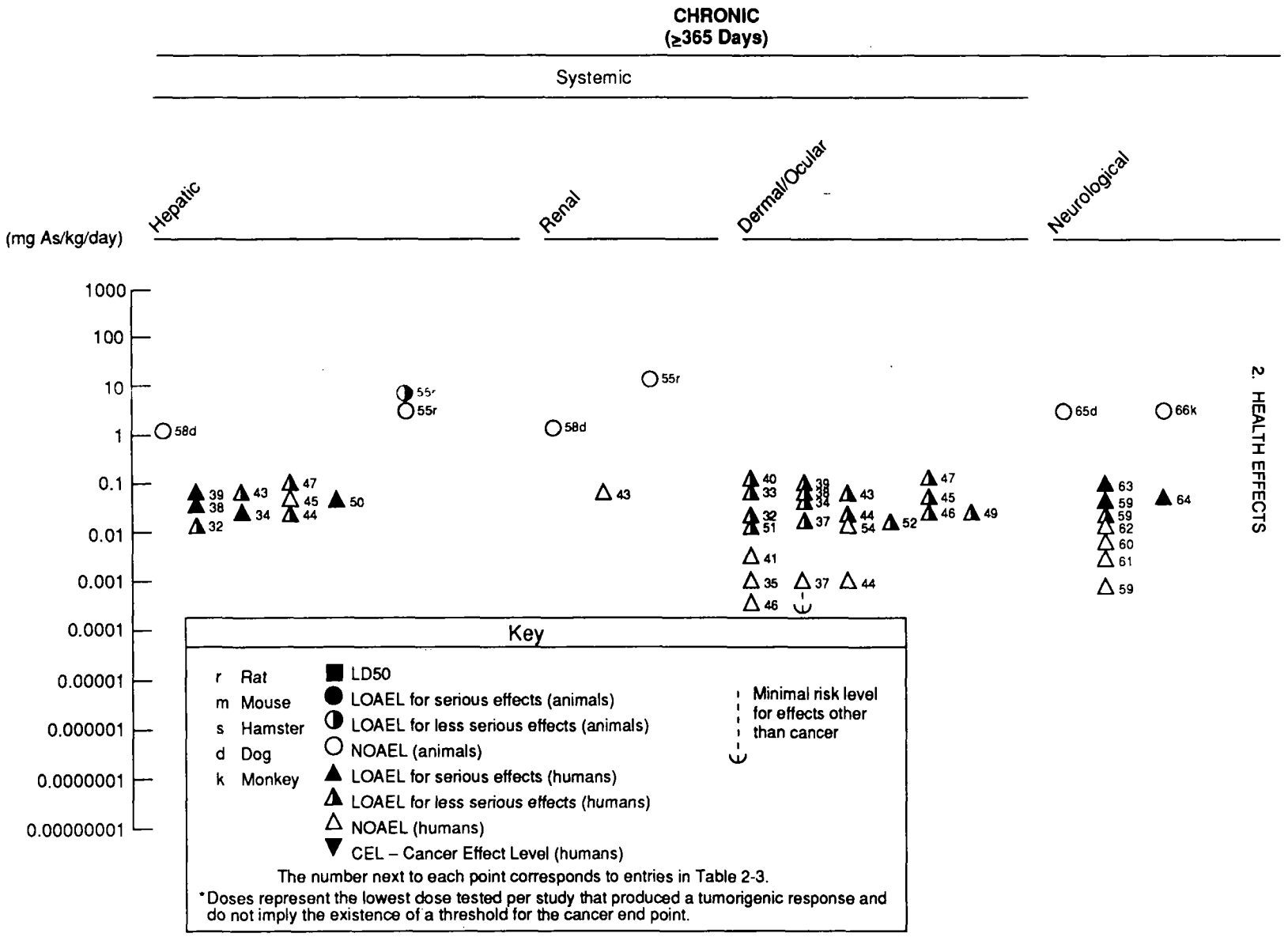


FIGURE 2-3. Levels of Significant Exposure to Inorganic Arsenic – Oral (Continued)

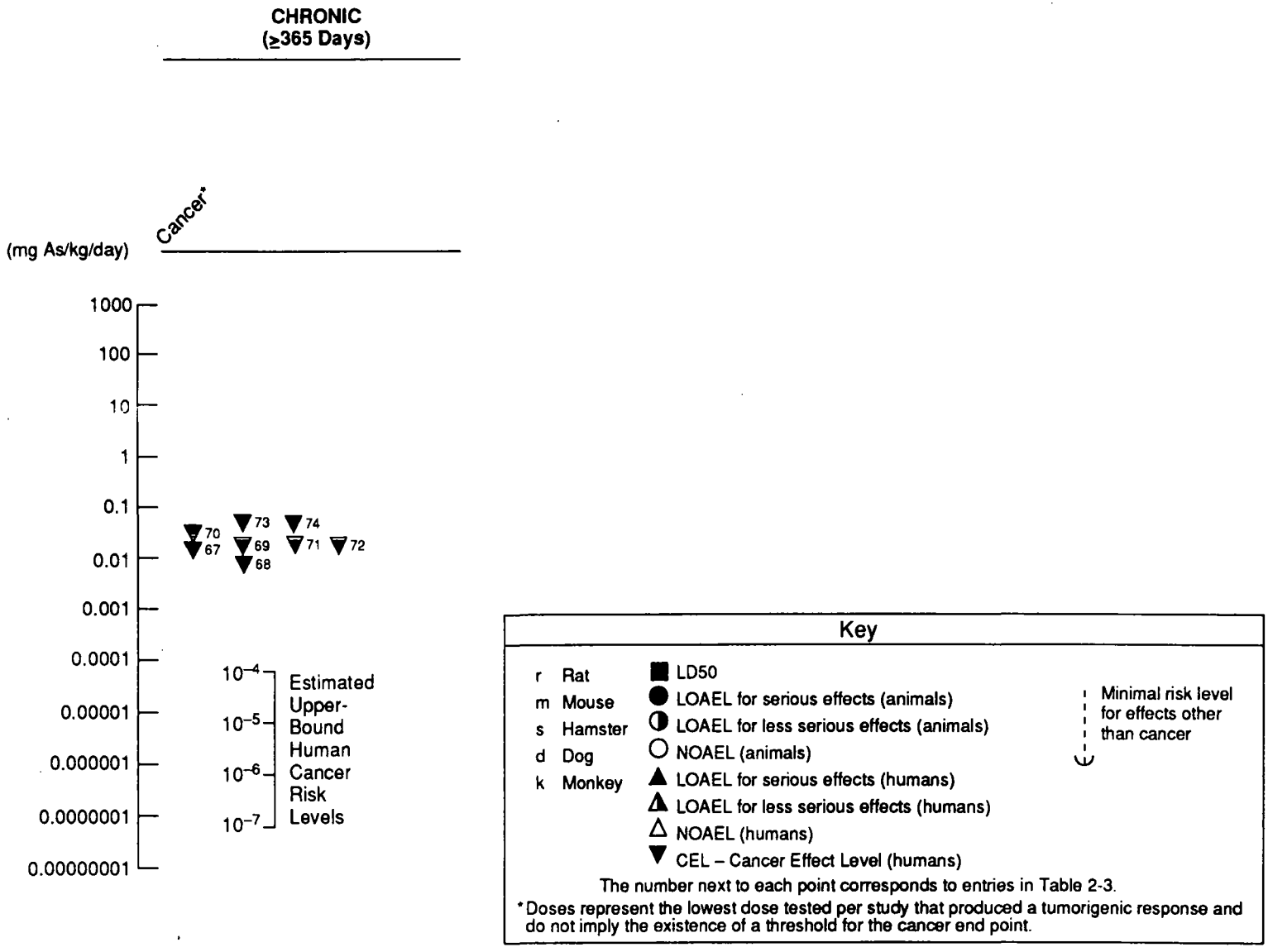


TABLE 2-4. Levels of Significant Exposure to Organic Arsenic - Oral

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (mg As/kg/day)	LOAEL (effect) Less serious (mg As/kg/day)	LOAEL (effect) Serious (mg As/kg/day)	Reference	Compound
ACUTE EXPOSURE									
Death									
1	Rat	(GO)	1 d 1x/d				23 (LD50 for females)	NTP 1989b	ROX
2	Rat	(GW)	1 d 1x/d				45 (LD50)	Kerr et al. 1963	ROX
3	Rat	(F)	14 d				22.8 (death in 8/10 rats)	NTP 1989b	ROX
4	Rat	(GW)	10 d 1x/d Gd 7-16				21.7 (1/37 died)	Rogers et al. 1981	DMA
5	Rabbit	(GW)	1 d 1x/d				50 (LD50)	Jaghabir et al. 1988	MMA
6	Mouse	(F)	14 d				37 (death in 7/10 mice)	NTP 1989b	ROX
7	Mouse	(GW)	10 d Gd 7-16 1x/d				217 (1/31 died)	Rogers et al. 1981	DMA
8	Mouse	(GO)	1 d 1x/d				69.5 (LD50 for females)	NTP 1989b	ROX
9	Mouse	(GW)	1 d 1x/d				650 (LD50 7days)	Kaise et al. 1989	DMA
10	Mouse	(GW)	1 d 1x/d				970 (LD50 7days)	Kaise et al. 1989	MMA
11	Dog	(GW)	1 d 1x/d				15 (LD50)	Kerr et al. 1963	ROX
Developmental									
12	Rat	(GW)	10 d 1x/d Gd 7-16		8.1		16.3 (malformed palates in 15%)	Rogers et al. 1981	DMA

TABLE 2-4. Levels of Significant Exposure to Organic Arsenic - Oral *(continued)*

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (mg As/kg/day)	LOAEL (effect) Less serious (mg As/kg/day)	LOAEL (effect) Serious (mg As/kg/day)	Reference	Compound
13	Mouse	(GW)	10 d Gd7-16 1x/d		109		217 (20% decrease in fetal weight, delayed ossification, cleft palate in 12/28)	Rogers et al. 1981	DMA
INTERMEDIATE EXPOSURE									
Death									
14	Rat	(F)	13 wk				5.8 (death in 10/12)	Kerr et al. 1963	ROX
15	Rat	(F)	13 wk				20 (death in 5/20)	NTP 1989b	ROX
16	Pig	(F)	28 d				5.8 (death in 2/18)	Edmonds and Baker 1986	ROX
Systemic									
17	Rat	(F)	10, 31, or 90 d	Hemato Hepatic Renal	5.7 5.7 1.4	5.7 (mild tubular degeneration)		NTP 1989b	ROX
18	Rat	(F)	13 wk	Renal			11.4 (tubular necrosis)	NTP 1989b; Abdo et al. 1989	ROX
19	Rat	(F)	42 d	Hemato Hepatic	1.11 1.11			Siewicki 1981	DMA
20	Rabbit	(GW)	40 d 1x/d	Gastro Hepatic Renal		2.3 (intestinal hyperemia) 2.3 (hepatocellular degeneration in 4/4) 2.3 (interstitial nephritis in 2/4)		Jaghabir et al. 1989	MMA
21	Mouse	(GW)	10 wk 1x/2d	Hemato	55			Prukop and Savage 1986	MMA
22	Mouse	(F)	13 wk	Hepatic	29.6			NTP 1989b	ROX
23	Mouse	(F)	9, 29 or 91 d	Hemato Renal	14.8 14.8			NTP 1989b	ROX

TABLE 2-4. Levels of Significant Exposure to Organic Arsenic - Oral *(continued)*

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (mg As/kg/day)	LOAEL (effect) Less serious (mg As/kg/day)	LOAEL (effect) Serious (mg As/kg/day)	Reference	Compound
Neurological									
24	Rat	(F)	13 wk				11.4 (ataxia, excitability)	NTP 1989b	ROX
25	Pig	(F)	28 d		1.44		2.9 (muscle tremors)	Edmonds and Baker 1986	ROX
26	Pig	(F)	30 d				0.87 (seizures in 100%)	Rice et al. 1985	ROX
27	Pig	(F)	30 d				0.87 (myelin degeneration)	Kennedy et al. 1986	ROX
Reproductive									
28	Mouse	(GW)	19 d 3d/wk				55 (reduced male fertility)	Prukop and Savage 1986	MMA

[a]The number corresponds to entries in Figure 2-4.

d = day(s); DMA = dimethylarsinic acid; (F) = feed; Gastro = gastrointestinal; Gd = gestation day; (GO) = gavage oil; (GW) = gavage water; Hemato = hematological; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; MMA = monomethylarsonic acid; NOAEL = no-observed-adverse-effect level; ROX = roxarsone; wk = week(s); x = time(s)

FIGURE 2-4. Levels of Significant Exposure to Organic Arsenic – Oral

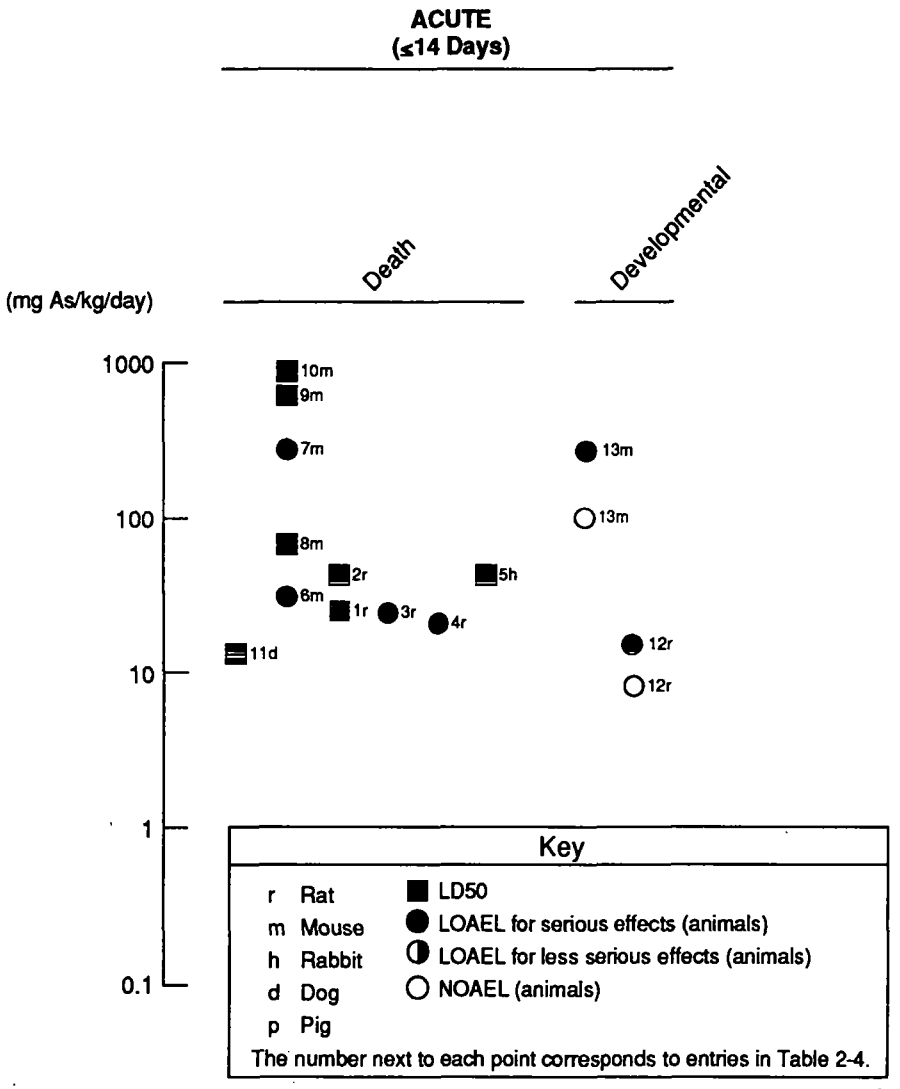
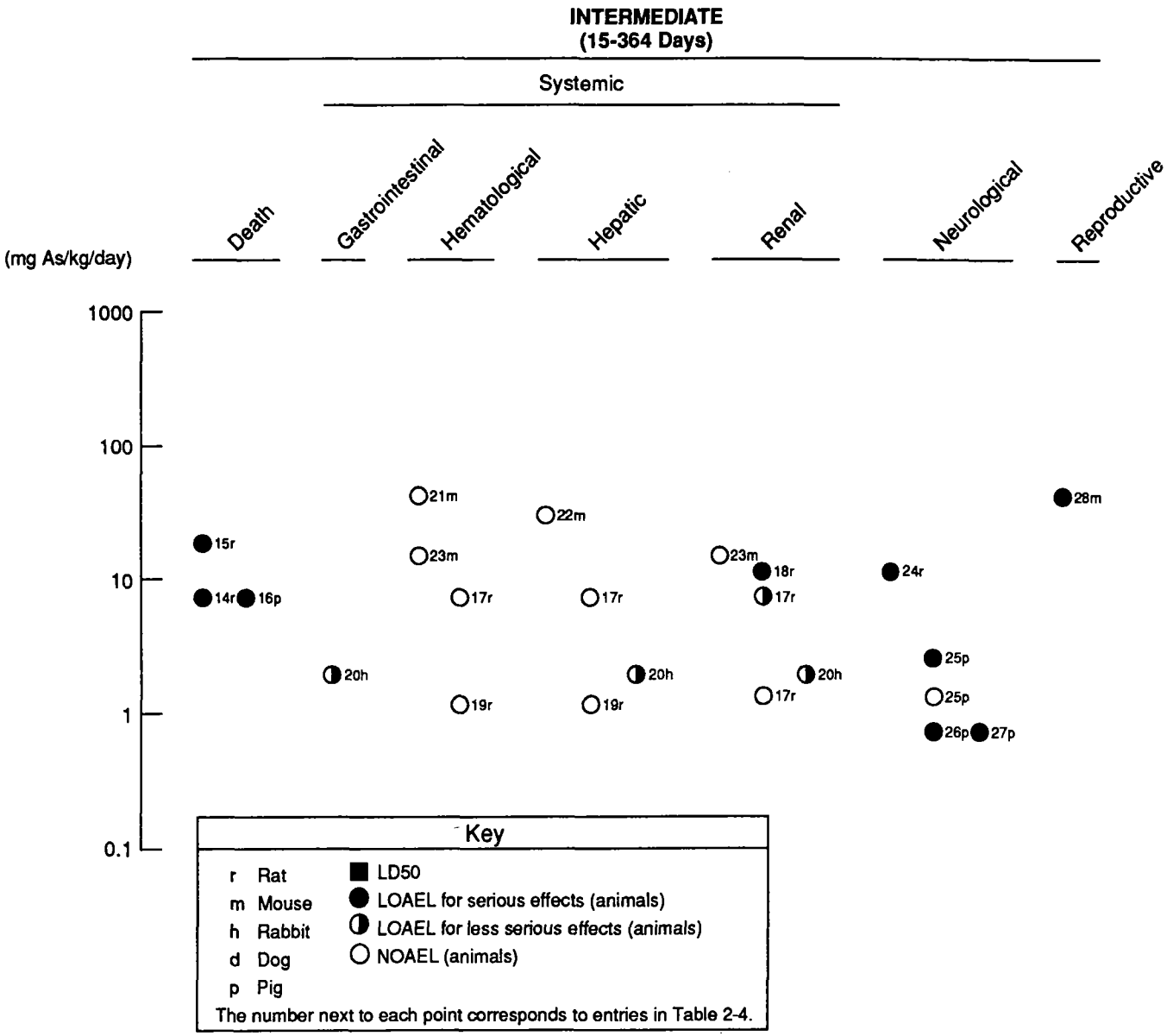


FIGURE 2-4. Levels of Significant Exposure to Organic Arsenic – Oral (Continued)



2.2.2.1 Death

Inorganic Arsenicals

There are many case reports of death in humans due to ingestion of high doses of arsenic. In nearly all cases, the most immediate effects are vomiting, diarrhea, and gastrointestinal hemorrhage, and death may ensue from fluid loss and circulatory collapse (Levin-Scherz et al. 1987; Saady et al. 1989). In other cases, death may be delayed and result from the multiple tissue injuries produced by arsenic (Campbell and Alvarez 1989). A precise estimate of the ingested dose is usually not available in acute poisonings, so quantitative information on lethal dose in humans is sparse. Two people in a family of eight died from ingestion of water containing about 110 ppm of arsenic (Armstrong et al. 1984). This corresponded to a dose of about 2 mg As/kg/day. Based on a review of clinical reports in the older literature, Holland (1904) estimated the minimum lethal dose to be about 130 mg (also about 2 mg/kg). A similar estimate of 70–180 mg (about 1–3 mg/kg) was provided by Vallee et al. (1960).

Lethal doses in animals are somewhat higher than the estimated lethal dose in humans. For example, acute LD_{50} values for arsenate and arsenite in rats and mice range from 15 to 110 mg As/kg (Dieke and Richter 1946; Gaines 1960; Harrisson et al. 1958; Kaise et al. 1985). Most deaths occurred within 1 day of exposure, but no details on the cause of death were reported. Data on lethality from repeated exposures are sparse, but average chronic exposures of about 3 mg As/kg/day as arsenate or arsenite have been noted to cause death in dogs (Byron et al. 1967) and monkeys (Heywood and Sortwell 1979).

Reliable LOAEL and LD_{50} values for lethality from oral exposure to inorganic arsenicals in each species and duration category are recorded in Table 2-3 and plotted in Figure 2-3.

Organic Arsenicals

No studies were located regarding death in humans after oral exposure to organic arsenicals, but the acute lethality of MMA, DMA, and roxarsone have been investigated in several animal studies. As shown in Table 2-4 and Figure 2-4, most acute lethal values range from about 15 to 70 mg As/kg (Jaghabir et al. 1988; Kerr et al. 1963; NTP 1989b; Rogers et al. 1981), although one study (Kaise et al. 1989) reported somewhat higher values (650–970 mg As/kg) for MMA and DMA in mice. The cause of death was not investigated in any of these studies. Intermediate-duration exposure to roxarsone caused death in pigs and rats at exposure levels of 5.8–20 mg As/kg/day (Edmonds and Baker 1986; Kerr et al. 1963; NTP 1989b).

2.2.2.2 Systemic Effects

The highest NOAEL values and all reliable NOAEL values for systemic effects from oral exposure in each species and duration category are recorded in Table 2-3 and plotted in Figure 2-3. Similar data for oral exposure to organic arsenicals are shown in Table 2-4 and plotted in Figure 2-4.

Respiratory Effects

Inorganic Arsenicals

Ingestion of arsenic by humans is usually not associated with serious injury to the respiratory system, although pulmonary edema and hemorrhagic bronchitis may occur in moderate to severe cases (e.g., Campbell and Alvarez 1989; Fincher and Koerker 1987). It is possible that this is primarily a secondary effect due to injury

to the pulmonary vasculature (see Cardiovascular Effects, below), although there are no studies specifically on this point. No respiratory effects were noted in dogs or rats after chronic oral exposure to arsenate or arsenite (Byron et al. 1967).

Organic Arsenicals

No studies were located regarding respiratory effects in humans or animals after oral exposure to organic arsenicals.

Cardiovascular Effects

Inorganic Arsenicals

A number of studies in humans indicate that arsenic ingestion may lead to serious effects on the cardiovascular system. Characteristic effects on the heart from both acute and long-term exposure include altered myocardial depolarization (prolonged Q-T interval, nonspecific S-T segment changes) and cardiac arrhythmias (Glazener et al. 1968; Goldsmith and From 1986; Heyman et al. 1956; Little et al. 1990; Mizuta et al. 1956). Long-term low-level exposures may also lead to damage to the vascular system. The most dramatic example of this is "Blackfoot disease," a condition that is endemic in an area of Taiwan where average drinking water levels of arsenic range from 0.17 to 0.80 ppm (Tseng 1977), corresponding to doses of about 0.014 to 0.065 mg As/kg/day (Abernathy et al. 1989). The disease is characterized by a progressive loss of circulation in the hands and feet, leading ultimately to necrosis and gangrene (Chen et al. 1988b; Chi and Blackwell 1968; Tseng 1977, 1989; Tseng et al. 1968). Several researchers have presented evidence that other factors besides arsenic (e.g., other water contaminants, dietary deficits) may play a role in the etiology of this disease (Ko 1986; Lu et al. 1990; Yu et al. 1984). While this may be true, the clear association between the occurrence of Blackfoot disease and the intake of elevated arsenic levels indicates that arsenic is at least a contributing factor. Moreover, effects of arsenic on the vascular system have also been reported in a number of other populations. For example, studies in Chile indicate that ingestion of 0.6–0.8 ppm arsenic in drinking water (corresponding to doses of 0.02–0.06 mg As/kg/day, depending on age) increase the incidence of Raynaud's disease and of cyanosis of fingers and toes (Borgono and Greiber 1972; Zaldivar 1977; Zaldivar and Guillier 1977). Autopsy of five children from this region who died of apparent arsenic toxicity showed a marked thickening of small and medium sized arteries in tissues throughout the body, especially the heart (Rosenberg 1974). Likewise, thickening and vascular occlusion of blood vessels were noted in German vintners exposed to arsenical pesticides in wine (Roth 1957). Similar alterations in vascular reactivity have been noted in rats given repeated oral doses of arsenic trioxide (11 mg As/kg/day) for several weeks (Bekemeier and Hirschelmann 1989), although no histological effects could be detected in the hearts of rats or dogs exposed to arsenate or arsenite for 2 years (Byron et al. 1967).

Organic Arsenicals

No studies were located regarding cardiovascular effects in humans or animals after oral exposure to organic arsenicals.

Gastrointestinal Effects

Inorganic Arsenicals

Clinical signs of gastrointestinal irritation, including nausea, vomiting, diarrhea, and abdominal pain, are observed in essentially all cases of acute high-dose exposures to inorganic arsenic (e.g., Armstrong et al. 1984; Campbell

and Alvarez 1989; Fincher and Koerker 1987; Franzblau and Lilis 1989; Goebel et al. 1990; Levin-Scherz et al. 1987). Similar signs are also frequently observed in groups or individuals with longer-term lower-dose exposures (e.g., Borgono and Greiber 1972; Cebrian et al. 1983; Franzblau and Lilis 1989; Holland 1904; Huang et al. 1985; Mazumder et al. 1988; Mizuta et al. 1956; Nagai et al. 1956; Silver and Wainman 1952; Wagner et al. 1979), but effects are usually not detectable at exposure levels below about 0.01 mg As/kg/day (Harrington et al. 1978; Valentine et al. 1985). These symptoms generally decline within a short time after exposure ceases. Similar signs of gastrointestinal irritation have been observed in studies in monkeys given a complex arsenate salt for 2 weeks (Heywood and Sortwell 1979), although no histological evidence of gastrointestinal injury was detected in rats or dogs exposed to arsenate or arsenite for 2 years (Byron et al. 1967).

Organic Arsenicals

No studies were located regarding gastrointestinal effects in humans after oral exposure to organic arsenicals. One study in rabbits indicates that the intestinal wall may be irritated and weakened by repeated intake of MMA (Jaghabir et al. 1989), but this one observation is not enough to support a firm conclusion.

Hematological Effects

Inorganic Arsenicals

Anemia and leukopenia are common effects of arsenic poisoning in humans, and have been reported following acute (Armstrong et al. 1984; Fincher and Koerker 1987), intermediate (Franzblau and Lilis 1989; Goldsmith and From 1986; Heyman et al. 1956; Mizuta et al. 1956; Westhoff et al. 1975), and chronic oral exposures (Glazener et al. 1968; Kyle and Pease 1965; Nagai et al. 1956; Tay and Seah 1975). These effects may be due to both a direct cytotoxic or hemolytic effect on the blood cells (Armstrong et al. 1984; Fincher and Koerker 1987; Goldsmith and From 1986; Kyle and Pease 1965; Lerman et al. 1980) and a suppression of erythropoiesis (Kyle and Pease 1965; Lerman et al. 1980). Hematological effects are usually not observed in humans exposed to levels of 0.07 mg As/kg/day or less (Harrington et al. 1978; Huang et al. 1985; Silver and Wainman 1952; Southwick et al. 1981), although intermediate-duration exposure to 0.05 mg/kg/day resulted in mild anemia in one study (Mizuta et al. 1956).

Hematological effects of ingested arsenic have not been thoroughly studied in laboratory animals, but no hematological effects have been detected in monkeys exposed to arsenate for 2 weeks (Heywood and Sortwell 1979), or in rats or dogs exposed to arsenate or arsenite for 1–2 years (Byron et al. 1967; Kroes et al. 1974; Schroeder et al. 1968). Rats exposed to arsenate for 6 weeks or more had decreased activities of several enzymes involved in heme synthesis, but data were not provided on whether this resulted in anemia (Woods and Fowler 1977, 1978).

Organic Arsenicals

No studies were located regarding hematological effects in humans after oral exposure to organic arsenicals. Several studies in rats and mice have not detected any significant hematological effects from repeated exposure (6–13 weeks) to MMA (Prukop and Savage 1986), DMA (Siewicki 1981), or roxarsone (NTP 1989b) at doses of 1.1–55 mg As/kg/day. These data suggest that oral exposure to organic arsenicals is unlikely to cause hematological effects, but this is not certain.

Musculoskeletal Effects

Inorganic Arsenicals

No studies were located regarding musculoskeletal effects in humans or animals after oral exposure to inorganic arsenicals.

Organic Arsenicals

No studies were located regarding musculoskeletal effects in humans or animals after oral exposure to organic arsenicals.

Hepatic Effects

Inorganic Arsenicals

A number of studies in humans exposed to inorganic arsenic by the oral route have noted signs or symptoms of hepatic injury. Clinical examination often reveals that the liver is swollen and tender (Chakraborty and Saha 1987; Franklin et al. 1950; Mazumder et al. 1988; Mizuta et al. 1956; Silver and Wainman 1952; Wade and Frazer 1953), and analysis of blood sometimes shows elevated levels of hepatic enzymes (Armstrong et al. 1984; Franzblau and Lilis 1989). These effects are most often observed after chronic exposure to doses of 0.019–0.1 mg As/kg/day (Chakraborty and Saha 1987; Franklin et al. 1950; Mazumder et al. 1988; Silver and Wainman 1985; Wade and Frazer 1953), but may also occur after acute exposures to higher doses (Armstrong et al. 1984). Histological examination of the livers of persons chronically exposed to similar doses has revealed a consistent finding of portal tract fibrosis (Mazumder et al. 1988; Morris et al. 1974; Piontek et al. 1989; Szuler et al. 1979), leading in some cases to portal hypertension and bleeding from esophageal varices (Szuler et al. 1979). Several researchers consider that these hepatic effects are secondary to damage to the hepatic blood vessels (Morris et al. 1974; Rosenberg 1974), but this is not directly established. Studies in dogs have not detected clinically significant hepatic injury following exposure to either arsenite or arsenate (Byron et al. 1967; Neiger and Osweiler 1989), although enlargement of the common bile duct was noted in rats given either arsenate or arsenite for 2 years (Byron et al. 1967).

Organic Arsenicals

No studies were located regarding hepatic effects in humans after oral exposure to organic arsenicals. Some small fluctuations in liver weight have been noted in rats and mice given repeated oral doses of roxarsone (NTP 1989b), but the toxicological significance of this is not clear. Histological examination of liver from rabbits given repeated oral doses of MMA showed diffuse inflammation and hepatocellular degeneration (Jaghabir et al. 1989), but the lesions were not severe. No effects were observed in rats exposed to DMA (Siewicki 1981). These data suggest that organic arsenicals may cause mild injury to the liver, but the data are too limited to draw firm conclusions.

Renal Effects

Inorganic Arsenicals

Most case studies of acute and chronic arsenic toxicity do not report clinical signs of significant renal injury, even when other systems are severely impaired (e.g., Franzblau and Lilis 1989; Jenkins 1966; Kersjes et al. 1987;

Mizuta et al. 1956; Silver and Wainman 1952). In some cases, elevated serum levels of creatinine or bilirubin have been noted (Armstrong et al. 1984; Levin-Scherz et al. 1987), and mild proteinuria may occur (Armstrong et al. 1984; Glazener et al. 1968; Tay and Seah 1975). In rare cases, renal failure may occur (e.g., Fincher and Koerker 1987), probably as a result of fluid imbalances or vascular injury. Studies in animals also indicate that the kidney is not a major target organ (Byron et al. 1967; Schroeder and Balassa 1967; Woods and Southern 1989), although some mild histological changes in renal tubules of monkeys exposed to arsenate for 2 weeks was noted by Heywood and Sortwell (1979), and some mild alterations in renal mitochondria in rats exposed to arsenate for 6 weeks were noted by Brown et al. (1976). These data suggest that the kidney is relatively less sensitive to arsenic than most other organ systems, and renal effects are unlikely to be of concern except secondary to fluid imbalances or cardiovascular injury.

Organic Arsenicals

No studies were located on renal effects in humans after oral exposure to organic arsenicals. Tubular degeneration and necrosis have been noted in rats (but not mice) given repeated oral doses of roxarsone (Abdo et al. 1989; NTP 1989b), and interstitial nephritis and tubular nephrosis have been noted in rabbits given repeated oral doses of MMA (Jaghabir et al. 1989). These data suggest that organic arsenicals can lead to significant renal injury, although the minimal dose is not well defined.

Dermal/Ocular Effects

Inorganic Arsenicals

One of the most common and characteristic effects of arsenic ingestion is a pattern of skin changes that include generalized hyperkeratosis and formation of hyperkeratotic warts or corns on the palms and soles, along with areas of hyperpigmentation interspersed with small areas of hypopigmentation on the face, neck, and back. These effects have been noted in a large majority of human studies involving intermediate- or chronic-duration oral exposure (e.g., Bickley and Papa 1989; Borgono and Greiber 1972; Borgono et al. 1980; Cebrian et al. 1983; Chakraborty and Saha 1987; Franklin et al. 1950; Franzblau and Lilis 1989; Huang et al. 1985; Luchtrath 1983; Mazumder et al. 1988; Nagai et al. 1956; Saha and Poddar 1986; Silver and Wainman 1952; Szuler et al. 1979; Tay and Seah 1975; Tseng et al. 1968; Wade and Frazer 1953; Wagner et al. 1979; Zaldivar 1974, 1977). In cases of low-level chronic exposure (usually from water), these skin lesions appear to be the most sensitive indication of effect, so this end point is considered to be the most appropriate basis for establishing a chronic oral MRL. However, other effects (hepatic injury, vascular disease, neurological effects) also appear to have similar thresholds. As shown in Table 2-3 and Figure 2-3, numerous studies in humans have reported dermal effects at chronic dose levels ranging from about 0.01–0.1 mg As/kg/day (Bickley and Papa 1989; Borgono and Greiber 1972; Borgono et al. 1980; Cebrian et al. 1983; Chakraborty and Saha 1987; Franklin et al. 1950; Huang et al. 1985; Luchtrath 1983; Mazumder et al. 1988; Piontek et al. 1989; Silver and Wainman 1952; Tseng et al. 1968; Zaldivar 1974, 1977). Several epidemiological studies of moderately-sized populations (20–200 people) exposed to arsenic through drinking water have detected no dermal or other effects at average chronic doses of 0.0004–0.01 mg As/kg/day (Cebrian et al. 1983; Harrington et al. 1978; Mazumder et al. 1988; Southwick et al. 1981; Valentine et al. 1985), and one very large study (based on 17,000 people) detected no effects in any person at an average total daily intake (from water plus food) of 0.0008 mg As/kg/day (Tseng et al. 1968). This value has been used to calculate a chronic oral MRL for inorganic arsenic of 0.0003 mg/kg/day, as described in footnote b in Table 2-3. An uncertainty factor of 10 was not required since the NOAEL is based on a relatively large human study. An uncertainty factor of 3 was selected to account for both the lack of data to preclude reproductive toxicity as a critical effect and to account for some uncertainty in whether the NOAEL of the critical study accounts for all sensitive individuals (IRIS 1992).

Another prominent dermal effect associated with chronic ingestion of inorganic arsenic is skin cancer. As discussed in greater detail in Section 2.2.2.8 (below), some of these skin cancers may evolve from the hyperkeratotic corns or warts, while the areas of altered pigmentation are not considered to be precancerous (EPA 1988e).

Dermal lesions similar to those observed in humans have not been noted in oral exposure studies in monkeys (Heywood and Sortwell 1979), dogs (Byron et al. 1967), or rodents (Schroeder et al. 1968).

Organic Arsenicals

No studies were located regarding dermal/ocular effects in humans or animals after oral exposure to organic arsenicals.

2.2.2.3 Immunological Effects

Inorganic Arsenicals

No studies were located regarding immunological effects in humans after oral exposure to inorganic arsenicals. No evidence of immunosuppression was detected in mice exposed to arsenate at levels up to 100 ppm (20 mg As/kg/day) (Kerkvliet et al. 1980).

Organic Arsenicals

No studies were located regarding immunological effects in humans or animals after oral exposure to organic arsenicals.

2.2.2.4 Neurological Effects

Inorganic Arsenicals

A large number of epidemiological studies and case reports indicate that ingestion of inorganic arsenic can cause injury to the nervous system. Acute, high-dose exposures (1 mg As/kg/day or above) often lead to encephalopathy, with signs and symptoms such as headache, lethargy, mental confusion, hallucination, seizures, and coma (Armstrong et al. 1984; Danan et al. 1984; Fincher and Koerker 1987). Intermediate- and chronic-duration exposures to lower levels (0.019–0.5 mg As/kg/day) are typically characterized by a symmetrical peripheral neuropathy (Franzblau and Lilis 1989; Hindmarsh et al. 1977; Huang et al. 1985; Mizuta et al. 1956; Silver and Wainman 1952; Wagner et al. 1979). This neuropathy usually begins as a numbness in the hands and feet, but later may develop into a painful "pins and needles" sensation. Both sensory and motor nerves are affected, and muscle weakness often develops, sometimes leading to wrist-drop or ankle-drop (Chhuttani et al. 1967; Heyman et al. 1956). Histological examination of nerves from affected individuals reveals a dying-back axonopathy with demyelination (Goebel et al. 1990; Hindmarsh and McCurdy 1986). Some recovery may occur following cessation of exposure, but this is a slow process and recovery is usually incomplete (Fincher and Koerker 1987; LeQuesne and McLeod 1977; Murphy et al. 1981). No neurological effects could be detected in populations chronically exposed to doses of 0.01 mg As/kg/day or less (Harrington et al. 1978; Hindmarsh et al. 1977; Southwick et al. 1981; Valentine et al. 1985). Neurological effects have not been reported in dogs or monkeys chronically exposed to arsenate or arsenite by the oral route (Byron et al. 1967; Heywood and Sortwell 1979).

The highest NOAEL values and all reliable LOAEL values for neurological effects from inorganic arsenic in each species and duration category are recorded in Table 2-3 and plotted in Figure 2-3.

Organic Arsenicals

No studies were located regarding neurological effects in humans after oral exposure to organic arsenicals. However, several studies in pigs indicate that repeated oral doses of roxarsone (0.87–5.8 mg As/kg/day for 1 month) can cause significant neurotoxicity (Edmonds and Baker 1986; Rice et al. 1985). The main signs were muscle tremors, partial paralysis, and seizures. Histological examinations of the spinal cord revealed a time-dependent degeneration of myelin and axons (Kennedy et al. 1986). Such prominent signs of neurological effects were not detected in rats or mice exposed to roxarsone, although suggestive evidence of neurological effects (hyperexcitability, ataxia, trembling) was noted in rats at the highest dose (11.4 mg As/kg/day) (NTP 1989b). These data (shown in Table 2-4 and Figure 2-4) suggest that organic arsenicals (at least the phenyl arsenates) are neurotoxic at high doses.

2.2.2.5 Developmental Effects

Inorganic Arsenicals

Whether ingestion of inorganic arsenic may cause developmental effects in humans has not been extensively investigated. No overall association between arsenic in drinking water and congenital heart defects was detected in a case-control study in Boston (Zierler et al. 1988), although an association with one specific lesion (coarctation of the aorta) was noted. Due to the small number of cases, this association might be due to random variation. In a similar case-control study, a marginal association (not statistically significant) was noted between detectable levels of arsenic in drinking water and the occurrence of spontaneous abortion (Aschengrau et al. 1989). However, a similar association was noted for mercury, potassium, silica, and water hardness, and a decreased incidence of abortion was associated with sulfate, nitrate, and alkalinity. This pattern of divergent associations for multiple contaminants suggests that at least some of the apparent associations may be random, or may be due to covariation with other risk factors. Thus, neither of these studies provides convincing evidence that ingestion of arsenic, at least at the levels usually encountered in drinking water, causes developmental toxicity in humans.

Studies in animals, however, do support the view that high doses of ingested arsenic may be fetotoxic and weakly teratogenic. A low incidence (0.5–5%) of fetal malformations (mostly skeletal defects) was noted in mice exposed during pregnancy to 23–68 mg As/kg/day of sodium arsenite (Baxley et al. 1981; Hood et al. 1978). No teratogenicity was observed in hamsters exposed to 14 mg As/kg/day of sodium arsenite (Hood and Harrison 1982), but there was an increased incidence of fetal mortality, perhaps as a consequence of severe maternal toxicity (12–36% of the dams died) (Baxley et al. 1981; Hood and Harrison 1982). These studies (shown in Table 2-3 and Figure 2-3) indicate that the fetus may be affected by ingested arsenic, but suggest that the fetus is not more susceptible to arsenic than is the mother.

Organic Arsenicals

No studies were located regarding developmental effects in humans after oral exposure to organic arsenicals. However, effects on fetal development (malformed palate, reduced fetal weight, delayed ossification, increased fetal mortality) have been observed in rats and mice given repeated oral doses of DMA during gestation (Rogers et al. 1981). These findings (summarized in Table 2-4 and shown Figure 2-4) suggest that high doses of organic arsenicals may have significant developmental toxicity, but the data are too limited to draw broad conclusions.

2.2.2.6 Reproductive Effects

Inorganic Arsenicals

No studies were located regarding reproductive effects in humans after oral exposure to inorganic arsenicals, and only one study has been performed in animals. In this study (a three-generation study in mice given sodium arsenite in drinking water at an average dose of 1 mg As/kg/day), no significant effects were detected on a number of reproductive parameters, although a trend toward a decreased number of pups per litter and slightly altered male:female sex ratio were observed (Schroeder and Mitchener 1971). In the absence of any further data, it is difficult to judge whether these effects are either statistically or biologically significant.

Organic Arsenicals

No studies were located regarding reproductive effects in humans after oral exposure to organic arsenicals. Male and female mice dosed with MMA (55 mg As/kg/day) prior to mating and during pregnancy produced fewer litters than normal, an effect which was attributable mainly to decreased fertility of the males (Prukop and Savage 1986). This observation (shown in Figure 2-4 and summarized in Table 2-4) suggests that spermatogenesis or sperm function might be impaired by organic arsenicals, but this was not studied directly.

2.2.2.7 Genotoxic Effects

Inorganic Arsenicals

Investigations of genotoxic effects of ingested arsenic have yielded mixed results. In humans exposed to Fowler's solution (potassium arsenite, usually taken at a dose of about 0.3 mg As/kg/day [Holland 1904]), increased sister chromatid exchange but no increase in chromosomal aberrations was reported in one study (Burgdorf et al. 1977), while just the converse (increased aberrations but no increase in sister chromatid exchange) was reported in another (Nordenson et al. 1979). In animal studies, an increased incidence of chromosomal abnormalities was detected in rats given oral doses of sodium arsenate (4 mg As/kg/day) for 2–3 weeks (Datta et al. 1986), but no consistent increase in chromosomal aberrations was detected in bone marrow cells or spermatogonia from mice given sodium arsenite (about 50 mg As/kg/day) for up to 8 weeks (Poma et al. 1987). These studies suggest that ingested arsenic may cause chromosomal effects, but these data are too limited to draw a firm conclusion. Other genotoxicity studies on inorganic arsenicals are discussed in Section 2.4.

Organic Arsenicals

No studies were located regarding genotoxic effects in humans after oral exposure to organic arsenicals. An increased number of DNA strand breaks were detected in lung and other tissues of mice given oral doses of DMA (Yamanaka et al. 1989a), an effect which appeared to be related to the formation of some active oxygen species. These breaks were largely repaired within 24 hours, so the relevance with respect to health risk is uncertain. Other genotoxicity studies on organic arsenicals are discussed in Section 2.4.

2.2.2.8 Cancer

Inorganic Arsenicals

There is convincing evidence from a large number of epidemiological studies and case reports that ingestion of inorganic arsenic increases the risk of developing skin cancer (Bickley and Papa 1989; Cebrian et al. 1983;

Luchtrath 1983; Piontek et al. 1989; Sommers and McManus 1953; Tay and Seah 1975; Tseng 1977; Tseng et al. 1968; Zaldivar 1974; Zaldivar et al. 1981). The most common lesions are multiple squamous cell carcinomas, which appear to develop from some of the hyperkeratotic warts or corns described in Section 2.2.2.2. In addition, multiple basal cell carcinomas may occur, typically arising from cells not associated with hyperkeratinization. In most cases, skin cancer develops only after prolonged exposure, but several studies have reported skin cancer in people exposed for less than a year (Reymann et al. 1978; Wagner et al. 1979). Although both types of skin cancer can be removed surgically, they may develop into painful lesions that may be fatal if left untreated (Shannon and Strayer 1989).

A number of studies which identify CEL values in exposed humans are summarized in Table 2-3 and shown in Figure 2-3. The EPA has reviewed all studies that provide dose-response data on the risk of skin cancer (EPA 1988e), and has concluded that the most reliable is the investigation by Tseng et al. (1968), in which the incidence of skin cancer was measured as a function of exposure level in over 40,000 people in Taiwan. Based on this study, the EPA calculated a unit risk (the upper-bound excess cancer risk from lifetime exposure to water containing 1 μg As/L) of $5x10^{-5}$ (IRIS 1992). The average daily doses (expressed as mg As/kg/day) that correspond to excess cancer risks of $1x10^{-4}$ to $1x10^{-7}$ are shown in Figure 2-3.

The relevance of cancer risk estimates derived from the Tseng et al. (1968) study to skin cancer risks in the United States occasionally has been questioned, based on concerns that there may have been significant exposure to arsenic from sources other than the well water (EPA 1987b), and that the dietary and socioeconomic characteristics of the exposed population are quite different from those of average U.S. citizens (EPA 1984a). Although these considerations may call the precise dose-response relationship observed in this study into question, they do not alter the conclusion that chronic arsenic ingestion is associated with increased risk of skin cancer.

Several epidemiological studies performed in the United States have not detected an increased frequency of skin cancer in small populations consuming water containing arsenic at levels of around 0.1–0.2 ppm (Goldsmith et al. 1972; Harrington et al. 1978; Morton et al. 1976; Southwick et al. 1981). These data suggest that arsenic-associated skin cancer is not a common problem in this country, but these studies lacked sufficient statistical power to detect small increases in skin cancer incidence that might have occurred at these low doses (Andelman and Barnett 1983).

In addition to the risk of skin cancer, there is mounting evidence that ingestion of arsenic may increase the risks of internal cancers as well. Many case studies have noted the occurrence of internal tumors of liver and other tissues in patients with arsenic-induced skin cancer (Falk et al. 1981b; Kasper et al. 1984; Koh et al. 1989; Lander et al. 1975; Regelson et al. 1968; Sommers and McManus 1953; Tay and Seah 1975; Zaldivar et al. 1981). These studies, suggestive but not convincing in their own right, are supported by more recent large-scale epidemiological studies in Taiwan, where clear associations and/or dose response trends have been detected for tumors of bladder, kidney, liver, and lung (Chen and Wang 1990; Chen et al. 1985, 1986, 1988a, 1988b, 1988c; Chiang et al. 1988; Wu et al. 1989). The EPA has not yet calculated a unit risk value or slope factor for arsenic-induced internal tumors.

Most studies of animals exposed to arsenate or arsenite by the oral route have not detected any clear evidence for an increased incidence of skin cancer or other cancers (Byron et al. 1967; Kroes et al. 1974; Schroeder et al. 1968). The basis for the lack of tumorigenicity in animals is not known, but could be related to species-specific differences in arsenic metabolism and distribution (see Section 2.3).

A few studies in mice have noted that arsenic ingestion may actually decrease the incidence of some tumor types. For example, arsenic exposure caused decreased incidence of urethane-induced pulmonary tumors (Blakley 1987), spontaneous mammary tumors (Schrauzer and Ishmael 1974; Schrauzer et al. 1976), and tumors resulting from injection of mouse sarcoma cells (Kerkvliet et al. 1980). However, arsenic also increased the growth rate of the tumors which did occur, resulting in a net decrease in survival time in tumor-bearing animals (Kerklviet et al. 1980; Schrauzer and Ishmael 1974). These observations suggest that arsenic may affect different types of neoplastic cells differently, perhaps acting mainly as a tumor promoter (Schrauzer and Ishmael 1974; Shirachi et al. 1987). However, these data do not suggest that arsenic should be viewed as having any net therapeutic "anti-cancer" effect.

Organic Arsenicals

No studies were located regarding cancer in humans after oral exposure to organic arsenicals. In an early 2-year study of roxarsone toxicity in animals, no increase in tumor frequency was detected in dogs given 1.5 mg As/kg/day, rats given 2.9 mg As/kg/day, or mice given 3.8 mg As/kg/day (Prier et al. 1963). More recently, lifetime studies of roxarsone at doses up to 1.4 mg As/kg/day yielded no evidence of carcinogenicity in male or female mice or female rats, but a slight increase in pancreatic tumors was noted in male rats (NTP 1989b). This was considered to constitute equivocal evidence of carcinogenicity. The incidence of basophilic foci (believed to be a precancerous lesion) in liver of rats initiated with diethylnitrosamine was increased by subsequent exposure to DMA, suggesting this compound could act as a cancer promoter (Johansen et al. 1984). These data are too limited to draw firm conclusions, but it appears that organic arsenicals might possess weak carcinogenic potential.

2.2.3 Dermal Exposure

Adverse effects from dermal exposure to inorganic or organic arsenicals have not been extensively investigated. Table 2-5 summarizes studies in animals and humans which provide quantitative data on dermal exposure-effect relationships for inorganic arsenicals. No quantitative data on dermal exposure to organic arsenicals were located. Available quantitative and qualitative data are discussed in greater detail below.

2.2.3.1 Death

Inorganic Arsenicals

No studies were located regarding death in humans after dermal exposure to inorganic arsenicals. In rats, no deaths resulted from dermal exposure to arsenate or arsenite at doses up to 1,000 mg As/kg (Gaines 1960). These data indicate that dermal exposure to inorganic arsenic compounds is very unlikely to result in death.

Organic Arsenicals

No studies were located regarding death in humans or animals after dermal exposure to organic arsenicals.

2.2.3.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, or renal effects in humans or animals after dermal exposure to inorganic or organic arsenicals.

TABLE 2-5. Levels of Significant Exposure to Inorganic Arsenic - Dermal

Species	Exposure duration/ frequency	System	NOAEL	LOAEL (effect) Less serious	LOAEL (effect) Serious	Reference	Valence
ACUTE EXPOSURE							
Systemic							
Gn pig	1 d 1x/d	Derm/oc	4000 mg As/L (As+5) 580 mg As/L (As+3)			Wahlberg and Boman 1986	As(+3) As(+5)
INTERMEDIATE EXPOSURE							
Systemic							
Mouse	18 wk 11x/wk	Derm/oc		2.5 mg As/kg (local hyperplasia, irritation)		Boutwell 1963	As(+3)

d = day(s); Derm/oc = dermal/ocular; Gn pig = guinea pig; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; wk = week(s); x = time(s)

Dermal/Ocular Effects

Inorganic Arsenicals

Several studies of humans exposed to arsenic dusts in the workplace have reported that inorganic arsenic (usually arsenic trioxide) can cause contact dermatitis (Holmqvist 1951; Pinto and McGill 1953). Typical responses included erythema and swelling, with papules and vesicles in more severe cases (Holmqvist 1951). The dermal contact rates that cause these effects in humans has not been quantified, but a similar direct irritation of the skin has been noted in mice exposed to 2.5 mg As/kg as sodium arsenite (Boutwell 1963). In contrast, no significant dermal irritation was noted in guinea pigs exposed to aqueous solutions containing 4,000 mg As/L as arsenate or 580 mg As/L as arsenite (Wahlberg and Boman 1986). These studies indicate that direct contact may be of concern at high exposure levels, but do not suggest that lower levels are likely to cause significant irritation.

Studies on possible dermal sensitization by inorganic arsenicals are discussed in Section 2.2.3.3 below.

Organic Arsenicals

Application of MMA to the skin of rabbits was reported to result in mild dermal irritation (Jaghabir et al. 1988), but too few details on dose, duration, or degree of irritation were provided to draw firm conclusions regarding the dermal or ocular irritancy of organic arsenicals.

2.2.3.3 Immunological Effects

Inorganic Arsenicals

Examination of workers exposed to arsenic trioxide dusts in a copper smelter led Holmqvist (1951) to suspect that repeated dermal contact could lead to dermal sensitization. In support of this, Holmqvist (1951) found a positive patch test in 80% of the exposed workers compared to 30% in a control population. These data do suggest that workers may be sensitized to arsenic, but the high response rate in controls seems unusual. A much lower response rate (0.5%) was noted in a more recent patch test study of dermal sensitization (Wahlberg and Boman 1986), and the few positive responses seemed to be due to a cross-reactivity with nickel. Studies in guinea pigs did not yield evidence of a sensitization reaction (Wahlberg and Boman 1986). Thus, there is some uncertainty whether the sensitization phenomenon reported by Holmqvist (1951) is of concern to nonoccupationally exposed individuals.

Organic Arsenicals

No studies were located regarding immunological effects in humans or animals after dermal exposure to organic arsenicals.

No studies were located regarding the following effects in humans or animals after dermal exposure to inorganic or organic arsenicals:

2.2.3.4 Neurological Effects
2.2.3.5 Developmental Effects
2.2.3.6 Reproductive Effects

2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.4.

2.2.3.8 Cancer

Inorganic Arsenicals

No studies were located regarding cancer in humans after dermal exposure to inorganic arsenicals. Application of arsenic acid to the skin of mice pretreated with dimethylbenzanthracene did not result in any skin tumors (Kurokawa et al. 1989), suggesting that arsenic does not act as a promoter in this test system.

Organic Arsenicals

No studies were located regarding cancer in humans or animals after dermal exposure to organic arsenicals.

2.3 TOXICOKINETICS

There is an extensive database on the toxicokinetics of inorganic arsenic. Most studies have been performed in animals, but there are a number of studies in humans as well. These studies reveal the following main points:

- Both arsenate and arsenite are well absorbed by both the oral and inhalation routes. Absorption by the dermal route has not been studied, but is probably quite low.
- Once absorbed, arsenites are partially oxidized to arsenates and arsenates are partially reduced to arsenites, yielding a mixture of As(+3) and As(+5) in the blood.
- The As(+3) form undergoes enzymic methylation in the liver to form MMA and DMA. The rate and relative proportion of methylation production varies among species.
- Most arsenic is promptly excreted in the urine as a mixture of As(+3), As(+5), MMA and DMA. Smaller amounts are excreted in feces. Some arsenic may remain bound to tissues, depending inversely on the rate and extent of methylation.

Less information is available for the organic arsenicals. It appears that both MMA and DMA are well absorbed, but are rapidly excreted in the urine and feces. MMA may be methylated to DMA, but neither MMA nor DMA are demethylated to yield inorganic arsenic.

A review of the evidence which supports these conclusions is presented below.

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

Since arsenic exists in air as particulate matter, absorption across the lung involves two processes: deposition of the particles onto the lung surface, and absorption of arsenic from the deposited material. In lung cancer patients exposed to arsenic in cigarette smoke, deposition was estimated to be about 40% and absorption was 75–85% (Holland et al. 1959). Thus, overall absorption (expressed as a percentage of inhaled arsenic) was about

30–34%. In workers exposed to arsenic trioxide dusts in smelters, the amount of arsenic excreted in the urine (the main route of excretion; see Section 2.3.4) was about 40–60% of the estimated inhaled dose (Pinto et al. 1976; Vahter et al. 1986). Although the percent deposition was not measured in these cases, it seems likely that nearly all of the deposited arsenic was absorbed. This conclusion is supported by intratracheal instillation studies in rats and hamsters, where clearance of oxy compounds of arsenic (sodium arsenite, sodium arsenate, arsenic trioxide) from the lung was rapid and nearly complete (60–90% within 1 day) (Marafante and Vahter 1987; Rhoads and Sanders 1985). In contrast, arsenic sulfide and lead arsenate were cleared more slowly (Marafante and Vahter 1987), indicating that the rate of absorption may be lower if the inhaled arsenic is in a highly insoluble form.

No studies were located regarding absorption of organic arsenicals in humans or animals after inhalation exposure. However, DMA instilled in the lungs of rats was absorbed very rapidly (half-time = 2.2 minutes) and nearly completely (at least 92%) (Stevens et al. 1977b). This indicates that organic arsenicals are likely to be well-absorbed by the inhalation route.

2.3.1.2 Oral Exposure

Several studies in humans indicate that arsenates and arsenites are well absorbed across the gastrointestinal tract. The most direct evidence is from measurement of fecal excretion in humans given oral doses of arsenite, where less than 5% was recovered in the feces (Bettley and O'Shea 1975). This indicates absorption was at least 95%. This is supported by studies in which urinary excretion in humans was found to account for 55–80% of daily oral intakes of arsenate or arsenite (Buchet et al 1981b; Crecelius 1977; Mappes 1977; Tam et al. 1979b). In contrast, ingestion of arsenic triselenide (As_2Se_3) did not lead to a measurable increase in urinary excretion (Mappes 1977), indicating that gastrointestinal absorption may be much lower if highly insoluble forms of arsenic are ingested.

These observations in humans are supported by a number of studies in animals. Fecal excretion of arsenates and arsenites ranged from 2–10% in monkeys and mice, with 70% or more appearing in urine (Charbonneau et al. 1978a; Vahter 1981; Vahter and Norin 1980). Hamsters appear to absorb somewhat less, since fecal excretion usually ranges from 10–40% (Marafante et al. 1987a; Marafante and Vahter 1987; Yamauchi and Yamamura 1985). As in humans, when highly insoluble arsenic compounds are administered (arsenic trisulfide, lead arsenate), gastrointestinal absorption is reduced (Marafante and Vahter 1987).

Based on urinary excretion studies in volunteers, it appears that both MMA and DMA are well-absorbed (at least 75–85%) across the gastrointestinal tract (Buchet et al. 1981a; Marafante et al. 1987b). This is supported by studies in animals, where at least 75% absorption has been observed for DMA (Marafante et al. 1987b; Stevens et al. 1977b; Yamauchi and Yamamura 1984) and MMA (Yamauchi et al. 1988).

2.3.1.3 Dermal Exposure

No quantitative studies were located on absorption of inorganic arsenicals in humans after dermal exposure. Uptake of arsenic into blood or tissues was undetectable for up to 24 hours in rats whose tails were immersed in solutions of sodium arsenate for 1 hour. However, arsenic began to increase in blood, liver, and spleen over the next 5 days (Dutkiewicz 1977). The rate of uptake was estimated to be 1–33 $\mu g/cm^2/hr$. These findings suggest that dermal exposure leads initially to arsenic binding to skin, and that the bound arsenic may slowly be taken up into the blood, even after exposure ends.

No studies were located on absorption of organic arsenicals in humans or animals after dermal exposure.

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

No studies were located on the distribution of arsenic in humans or animals after inhalation exposure, but intratracheal administration of arsenic trioxide to rats resulted in distribution of arsenic to liver, kidney, skeleton, gastrointestinal tract, and other tissues (Rhoads and Sanders 1985). This is consistent with data from oral and parenteral studies (below) which indicate that absorbed arsenic is distributed throughout the body.

No studies were located regarding the distribution of organic arsenicals in humans or animals after inhalation exposure. However, DMA administered to rats by the intratracheal route was distributed throughout the body (Stevens et al. 1977b), suggesting that inhalation of organic arsenicals would also lead to widespread distribution.

2.3.2.2 Oral Exposure

Analysis of tissues taken at autopsy from people who were exposed to background levels of arsenic in food and water revealed that arsenic is present in all tissues of the body (Liebscher and Smith 1968). Most tissues had about the same concentration level (0.05–0.15 ppm), while levels in hair (0.65 ppm) and nails (0.36 ppm) were somewhat higher. This indicates that there is little tendency for arsenic to accumulate preferentially in any internal organs. Similar results have been obtained in mice and hamsters given oral doses of arsenate or arsenite, where elevated levels of arsenic were found in all tissues examined (Vahter and Norin 1980; Yamauchi and Yamamura 1985), including the placenta and fetus of pregnant females (Hood et al. 1987, 1988).

No studies were located on the distribution of organic arsenicals in people following oral exposure, but MMA and DMA formed in vivo by methylation of inorganic arsenic in hamsters appears to be distributed to all tissues (Takahashi et al. 1988; Yamauchi and Yamamura 1985). This is supported by studies in animals, in which MMA and DMA were found in all tissues after acute oral doses (Stevens et al. 1977b; Yamauchi and Yamamura 1984; Yamauchi et al. 1988).

2.3.2.3 Dermal Exposure

No studies were located regarding distribution of inorganic or organic arsenicals in humans or animals after dermal exposure.

2.3.2.4 Other Routes of Exposure

Studies in mice, rabbits, and monkeys injected intravenously with solutions of arsenite or arsenate confirm that arsenic is widely distributed throughout the body (Lindgren et al. 1982; Marafante and Vahter 1986; Vahter and Marafante 1983; Vahter et al. 1982). Shortly after exposure, the concentration of arsenic tends to be somewhat higher in liver, kidney, lung, and gastrointestinal epithelium (Lindgren et al. 1982; Vahter and Marafante 1983; Vahter et al. 1982), but levels tend to equilibrate over time. Arsenate shows a tendency to deposit in skeletal tissue that is not shared by arsenite (Lindgren et al. 1982, 1984), presumably because arsenate is an analog of phosphate.

The distribution of arsenic in the rat is quite different from other animal species. In the rat, a large majority of the arsenic becomes bound to hemoglobin in red blood cells, and very little reaches other tissues (Lanz et al. 1950). For this reason, the rat is probably not an appropriate toxicokinetic model for distribution, metabolism, or excretion of arsenic by humans.

2.3.3 Metabolism

The metabolism of inorganic arsenic has been extensively studied in humans and animals. Two processes are involved: (1) reduction/oxidation reactions that interconvert arsenate and arsenite, and (2) methylation reactions, which convert arsenite to MMA and DMA. These processes appear to be similar whether exposure is by the inhalation, oral, or parenteral route.

The basic type of evidence which supports these conclusions is derived from analysis of urinary excretion products. Exposure of humans to either arsenates or arsenites is found to result in increased levels of inorganic As(+3), inorganic As(+5), MMA and DMA in urine (Buchet et al. 1981a, 1981b; Crecelius 1977; Lovell and Farmer 1985; Smith et al. 1977; Tam et al. 1979b; Vahter 1986). Similar results are obtained from studies in mice (Vahter 1981; Vahter and Envall 1983), hamsters (Hirata et al. 1988; Marafante and Vahter 1987; Takahashi et al. 1988), and rabbits (Maiorino and Aposhian 1985; Marafante et al. 1985; Vahter and Marafante 1983).

The relative proportions of As(+3), As(+5), MMA, and DMA in urine can vary depending upon the chemical administered, the time after exposure, the route of exposure, the dose level, and the exposed species. In general, however, DMA is the principal metabolite, with lower levels of inorganic arsenic (As+3 and As+5) and MMA. In humans, the relative proportions are usually about 40–60% DMA, 20–25% inorganic arsenic, and 15–25% MMA (Buchet et al. 1981a; Smith et al. 1977; Tam et al. 1979b; Vahter 1986). The rabbit has a similar ratio of metabolites (Maiorino and Aposhian 1985), suggesting that this may be the best animal model for toxicokinetics in humans. In contrast, the marmoset monkey does not methylate inorganic arsenic (Vahter and Marafante 1985; Vahter et al. 1982), and so is a poor model for humans.

Studies in vitro indicate that the substrate for methylation is As(+3), and that As(+5) is not methylated unless it is first reduced to As(+3) (Buchet and Lauwerys 1985, 1988; Lerman et al. 1983). The main site of methylation appears to be the liver, where the methylation process is mediated by enzymes that utilize S-adenosylmethionine as cosubstrate (Buchet and Lauwerys 1985, 1988). Under normal conditions, the availability of methyl donors (e.g., methionine, choline, cysteine) does not appear to be rate limiting in methylating capacity, either in humans (Buchet et al. 1982) or in animals (Buchet and Lauwerys 1987; Buchet et al. 1981a). However, severe dietary restriction of methyl donor intake can result in significant decreases in methylating capacity (Buchet and Lauwerys 1987; Vahter and Marafante 1987).

Since the methyl derivatives of arsenic appear to be less toxic than inorganic arsenic (see Section 2.2), and since methylation tends to result in lower tissue retention of inorganic arsenic (Marafante and Vahter 1984, 1986; Marafante et al. 1985; Vahter and Marafante 1987), the methylation process is usually viewed as a detoxification mechanism. Because methylation is an enzymic process, an important issue is the dose of arsenic that saturates the methylation capacity of an organism. Limited data from studies in humans suggest that methylation may begin to become limiting at doses of about 0.2–1 mg/day (0.003–0.015 mg/kg/day) (Buchet et al. 1981b; Marcus and Rispin 1988). However, these observations are relatively uncertain since they are based on data from only a few people, and the pattern of urinary excretion products in humans who ingested high (near lethal) oral doses or were exposed to elevated levels in the workplace is not much different from that in the general population (Lovell and Farmer 1985; Vahter 1986). Thus, the dose rate at which methylation capacity becomes saturated cannot be precisely defined with current data.

Organic arsenicals appear to undergo little metabolism. Humans who ingested a dose of MMA converted a small amount (about 13%) to DMA (Buchet et al. 1981a), and several studies in hamsters have noted the formation of low levels of the trimethyl derivative (trimethylarsine oxide, $(CH_3)_3AsO$) (Yamauchi and Yamamura

1984; Yamauchi et al. 1988). However, the methylarsenates are not demethylated to inorganic arsenic either in humans (Buchet et al. 1981a; Marafante et al. 1987b) or in animals (rats and hamsters) (Stevens et al. 1977b; Yamauchi and Yamamura 1984).

2.3.4 Excretion

2.3.4.1 Inhalation Exposure

As noted previously (see Section 2.3.1.1), urinary excretion of arsenic appears to account for 30–60% of the inhaled dose (Holland et al. 1959; Pinto et al. 1976; Vahter et al. 1986). Since the deposition fraction usually ranges from about 30–60% for most respirable particles (EPA 1989b), this suggests that nearly all arsenic that is deposited in the lung is excreted in the urine. The time course of excretion in humans exposed by inhalation has not been thoroughly investigated, but urinary arsenic levels in workers in a smelter rose within hours after they came to work on Monday, and then fell over the weekend (Vahter et al. 1986). This implies that excretion is fairly rapid, and this is supported by intratracheal studies in rats (Rhoads and Sanders 1985) and hamsters (Marafante and Vahter 1987), where whole body clearance of administered arsenate or arsenite occurred with a half-time of 1 day or less. However, small amounts of arsenic may remain bound in the lung, and only be cleared with a half-time of several months (Rhoads and Sanders 1985).

No studies were located regarding the excretion of organic arsenicals by humans or animals after inhalation exposure. However, rats that were given a single intratracheal dose of DMA excreted about 60% in the urine and about 8% in the feces within 24 hours (Stevens et al. 1977b). This indicates that organic arsenicals are likely to be promptly excreted after inhalation exposure.

2.3.4.2 Oral Exposure

Direct measurements of arsenic excretion in humans who ingested known amounts of arsenite or arsenate indicate that very little is excreted in the feces (Bettley and O'Shea 1975), and that 45–85% is excreted in urine within 1–3 days (Buchet et al. 1981a; Crecelius 1977; Mappes 1977; Tam et al. 1979b). A similar pattern is observed in hamsters (Yamauchi and Yamamura 1985; Marafante and Vahter 1987) and mice (Vahter and Norin 1980). Accordingly, whole body clearance is fairly rapid, with half-times of 40–60 hours in humans (Buchet et al. 1981b; Mappes 1977). Clearance is even more rapid in mice and hamsters, with 90% removed in two days (Marafante and Vahter 1987; Vahter 1981; Vahter and Norin 1980).

Studies in humans indicate that ingested MMA and DMA are excreted mainly in the urine (75–85%), and this occurs mostly within 1 day (Buchet et al. 1981a; Marafante et al. 1987b). This is supported by studies in rats and hamsters, although in animals excretion is more evenly distributed between urine and feces (Marafante et al. 1987b; Stevens et al. 1977b; Yamauchi and Yamamura 1984; Yamauchi et al. 1988).

2.3.4.3 Dermal Exposure

No studies were located regarding excretion of inorganic arsenicals in humans or animals following dermal exposure. In rats, arsenic absorbed through the tail was excreted approximately equally in urine and feces, similar to the excretion pattern following oral exposure (Dutkiewicz 1977).

No studies were located regarding excretion of organic arsenicals in humans or animals following dermal exposure.

2.3.4.4 Other Routes of Exposure

Excretion of arsenate and arsenite following parenteral exposure of animals is similar to that seen following oral exposure. In rabbits and mice, urinary excretion within 8 hours usually accounts for about 50–80% of the dose (Maehashi and Murata 1986; Maiorino and Aposhian 1985; Vahter and Marafante 1983). Somewhat lower levels (30–40%) are excreted in the urine of marmoset monkeys (Vahter and Marafante 1985; Vahter et al. 1982), probably because of the absence of methylation in this species. Whole-body clearance studies in mice indicate that arsenate is over 65% removed within 24 hours, while arsenite is about 86% removed at 24 hours (Lindgren et al. 1982).

2.4 RELEVANCE TO PUBLIC HEALTH

Arsenic is a potent toxicant that may exist in several valence states and in a number of inorganic and organic forms. Most cases of arsenic-induced toxicity in humans are due to exposure to inorganic arsenic, and there is an extensive database on the human health effects of the common arsenic oxides and oxyacids. Although there may be some differences in the potency of different chemical forms (e.g., arsenites tend to be somewhat more toxic than arsenates), these differences are usually minor and are not focused on in this profile.

Exposures of humans near hazardous waste sites could involve inhalation of arsenic dusts in air, ingestion of arsenic in water, food, or soil, or dermal contact with contaminated soil or water. By the inhalation route, the effect of greatest public health concern is increased risk of lung cancer, although respiratory irritation, nausea, and skin effects may also occur. As summarized in Table 2-1 and Figure 2-1 in Section 2.2.1 (above), there are only a few quantitative data on noncancer effects in humans exposed to inorganic arsenic by the inhalation route. However, it appears that such effects are unlikely below a concentration of about 0.1–1.0 mg As/m^3.

By the oral route, the effects most likely to be of human health concern are gastrointestinal irritation, peripheral neuropathy, vascular lesions, anemia, and a group of skin diseases, including skin cancer. As summarized in Table 2-3 and Figure 2-3 in Section 2.2.2 (above), most of the noncancer effects tend to occur at similar oral exposure levels, indicating that the dose-response curves for these effects are similar. For acute exposures, most reported LOAEL values are about 1 mg As/kg/day (see Figure 2-3). However, these data are mainly from case reports of fatal or near-fatal exposures, so it is likely that lower acute doses could also produce the characteristic signs of acute arsenic toxicity. For intermediate-duration exposure, most oral LOAELs range from about 0.05 to 0.5 mg As/kg/day, while chronic LOAELs range from about 0.01 to 0.1 mg As/kg/day, while chronic oral NOAEL values range from 0.0004 to 0.0009 mg As/kg/day (see Figure 2-3). Based on these data, the chronic oral MRL is estimated to be 0.0003 mg As/kg/day.

Relatively little information is available on effects due to direct dermal contact with inorganic arsenicals, but several studies indicate the chief effect is local irritation and dermatitis, with little risk of other adverse effects.

Humans may also be exposed to a variety of organic arsenicals (mainly methyl and phenyl derivatives of arsenic acid), since these are widely used in agriculture. Although human health effects data are sparse, it is generally considered that organic arsenicals are substantially less toxic than the inorganic forms. However, available data (mainly from animal studies) make clear that adequate doses of the methyl and phenyl arsenates can produce adverse health effects that resemble those of the inorganic arsenicals, and so the possibility of health risks from the organic arsenicals should not be disregarded.

Presented below are more detailed descriptions and discussions of the characteristic adverse effects of the inorganic and organic arsenicals most likely to be of concern to humans. These evaluations focus on human health effects data wherever possible, since most studies in animals suggest that animals are less sensitive to arsenic than humans. Animal data are presented when human data are lacking, but these data should be extrapolated to humans only with caution.

Death. There have been many reported cases of death in humans due to ingestion of inorganic arsenicals. Acute lethality is usually attributable to cardiopulmonary collapse (Levin-Scherz et al. 1987; Saady et al. 1989) while delayed lethality results from failure of one or more of the many tissues injured by arsenic (Campbell and Alvarez 1989). Estimates of the minimum lethal oral dose in humans range from 1-3 mg As/kg/day (Armstrong et al. 1984; Holland 1904; Vallee et al. 1960), although there may be considerable variation between individuals. Lethal oral doses are usually higher in animals (15-110 mg As/kg) (Gaines 1960; Harrisson et al. 1958), consistent with the general trend that animals are less sensitive to arsenic than humans. No cases were located regarding death in humans from inhalation exposure to inorganic arsenicals. The reason for this apparent route specificity is not clear, but might simply be due to lower exposure levels, or perhaps to toxicokinetic differences in exposure rate or arsenic metabolism. Dermal exposure to inorganic arsenicals has not caused lethality in humans, presumably because dermal absorption is very limited.

No cases of death in humans were located that are attributable to exposure to organic arsenicals, but studies in animals show that ingestion or inhalation of organic arsenicals (DMA, MMA, roxarsone) may be lethal. Fatal doses by the inhalation route are so high (above 2,000 mg As/m^3) (Stevens et al. 1979) as to be of no practical concern, while most oral and parenteral lethal doses range from 15 to 960 mg As/kg/day, depending on the compound and the animal species (Jaghabir et al. 1988; Kaise et al. 1989; NTP 1989b; Rogers et al. 1981; Stevens et al. 1979).

Systemic Effects

Respiratory Effects. Inhalation of inorganic arsenic dusts (usually containing mainly arsenic trioxide) is irritating to the nose, throat, and lungs, and can lead to hoarseness, bronchitis, and rhinitis (Dunlap 1921; Morton and Caron 1989). However, chronic functional impairment of respiration is not usually observed even in workers exposed to high levels of arsenic trioxide in air (Perry et al. 1948). Effects on the lung may actually be more pronounced following high dose (i.e., near-lethal) oral exposure, where edema and hemorrhagic lesions have been noted (Campbell and Alvarez 1989; Fincher and Koerker 1987). It seems possible that this is due mainly to an effect of ingested arsenic on pulmonary blood vessels rather than on alveolar cells, but this is not known with certainty. Respiratory effects are usually not listed among the symptoms in humans exposed to moderate or low oral doses of inorganic arsenic (e.g., Borgono and Greiber 1972; Chakraborty and Saha 1987; Mizuta et al. 1958), although specific functional or histological studies have not been performed in these groups.

The effects of organic arsenicals on the respiratory tract have not been well studied. There are no data by any route from human studies, but acute respiratory distress and lung injury have been reported in mice that inhaled very high levels of DMA (Stevens et al. 1979). Since only high exposures were investigated, it is not possible to compare the relative irritancy and respiratory toxicity of the organic and inorganic arsenicals.

Cardiovascular Effects. High oral doses of inorganic arsenic can lead to marked cardiac arrhythmias and altered electrocardiograms in humans (e.g., Glazener et al. 1968; Little et al. 1990). In severe cases, this can lead to premature ventricular contractions and ventricular tachycardia that require medical intervention (Goldsmith and From 1986), or may even result in death (Hall and Harruff 1989).

Chronic oral exposure to lower levels of inorganic arsenic can also result in serious damage to the vascular system. The most extreme manifestation of this is "Blackfoot disease," a progressive loss of circulation in the fingers and toes that ultimately leads to gangrene (Chen et al. 1988b; Chi and Blackwell 1968; Tseng et al. 1968). This disease has only been reported in one area of Taiwan, and it seems likely that other factors (e.g., fluorescent humic substances in the water) may contribute to the severity of the effect besides the elevated level of arsenic intake (Ko 1986; Lu et al. 1990; Yu et al. 1984). If so, Blackfoot disease per se may not be likely to occur in other areas, but less severe signs of vascular injury (Raynaud's disease, cyanosis of fingers and toes) have been noted in several other populations exposed to inorganic arsenic, both by inhalation (Lagerkvist et al. 1986, 1988) and by the oral route (Borgono and Greiber 1972; Roth 1957; Zaldivar 1977). The mechanism of this effect is not clear, but histological examination of blood vessels from exposed persons reveals an intimal thickening that may lead to vessel occlusion (Rosenberg 1974).

Possible myocardial or vascular effects have not been investigated for the organic arsenicals, either in humans or animals.

Gastrointestinal Effects. Nausea, vomiting, and diarrhea are very common symptoms in humans following oral exposure to inorganic arsenicals, both after acute high dose exposure (e.g., Armstrong et al. 1984; Levin-Scherz et al. 1987) and after repeated exposure to lower doses (e.g., Borgono and Greiber 1972; Mizuta et al. 1956). These effects are likely due mainly to a direct irritation of the gastrointestinal mucosa. Similar effects have also been observed following intermediate- or chronic-duration inhalation exposure (Beckett et al. 1986; Ide and Bullough 1988; Morton and Caron 1989), presumably because of the transfer of inhaled particulates from the respiratory tree to the stomach via mucociliary clearance. By either route, gastrointestinal symptoms usually wane within several days after exposure ceases (Mizuta et al. 1956).

The effects of organic arsenicals on the gastrointestinal tract have not been as thoroughly investigated. No reports were located of gastrointestinal complaints in humans exposed to organic arsenicals, but inhalation exposure of rats to high doses of DMA can cause diarrhea (Stevens et al. 1979), and oral exposure of rabbits to MMA can cause intestinal irritation and weakening of the intestinal wall (Jaghabir et al. 1989). These data suggest that the organic arsenicals are capable of producing gastrointestinal effects similar to the inorganic arsenicals, but the data are too sparse to make quantitative comparisons.

Hematological Effects. Anemia is often observed in humans exposed to arsenic by the oral route (e.g., Armstrong et al. 1984; Glazener et al. 1968; Mizuta et al. 1956; Westhoff et al. 1975). This is probably due mainly to a toxic effect on the erythropoietic cells of bone marrow (Franzblau and Lilis 1989; Lerman et al. 1980; Westhoff et al. 1975), although increased hemolysis may also contribute (Goldsmith and From 1986; Kyle and Pease 1975). Leukopenia is also common in cases of oral exposure to inorganic arsenicals (e.g., Armstrong et al. 1984; Franzblau and Lilis 1989; Kyle and Pease 1965). Similar depression of red or white blood cells has not been reported in workers exposed by the inhalation route (e.g., Beckett et al. 1986; Bolla-Wilson and Bleecker 1987; Ide and Bullough 1988; Morton and Caron 1989). As discussed above, the reason for this is not clear, but may be simply a function of dose.

Information on possible hematological effects of organic arsenicals is sparse. No effects were observed in humans exposed to arsanilic acid (Watrous and McCaughey 1945), and no effects were detected in animals exposed to MMA, DMA, or roxarsone (NTP 1989b; Prukop and Savage 1986; Siewicki 1981). These data suggest that the organic arsenicals have low hematotoxicity, but the data are too limited to draw firm conclusions, particularly for humans.

Hepatic Effects. Oral exposure of humans to inorganic arsenicals often produce a swollen and tender liver (e.g., Chakraborty and Saha 1987; Mazumder et al. 1988; Mizuta et al. 1956; Silver and Wainman 1952; Wade and Frazer 1953). However, there is usually only marginal evidence of hepatic cell injury (e.g., elevated serum enzyme levels) (Armstrong et al. 1984; Franzblau and Lilis 1989), and histological examination suggests that the principal lesion is a portal tract fibrosis and cirrhosis that results in portal hypertension (Franklin et al. 1950; Mazumder et al. 1988; Morris et al. 1974; Szuler et al. 1979). Thus, the hepatic effects may be largely vascular in origin. Similar hepatic effects have not been noted in workers exposed to inorganic arsenic by the inhalation route (Bolla-Wilson and Bleecker 1987; Ide and Bullough 1988).

No information was located on hepatotoxic effects of organic arsenicals in humans, although some mild effects on liver weight and histological appearance have been detected in rats and mice given repeated oral doses of roxarsone (NTP 1989b) and rabbits given MMA (Jaghabir et al. 1989). These data are too limited to judge whether the organic arsenicals act on the liver similarly to inorganic arsenic.

Renal Effects. Signs of renal injury are usually mild or absent in cases of humans exposed to inorganic arsenic either by the oral route (Armstrong et al. 1984; Jenkins 1966; Mizuta et al. 1956) or by the inhalation route (Bolla-Wilson and Bleecker 1987; Ide and Bullough 1988). These observations suggest that the kidney is relatively less sensitive to inorganic arsenic than other systemic target tissues, and that renal effects are unlikely to be of major human health concern.

No information was located on renal effects of organic arsenicals in humans, but histological signs of tubular damage have been noted in rats given repeated oral doses of roxarsone (NTP 1989b) and in rabbits given repeated oral doses of MMA (Jaghabir et al. 1989). This suggests that the organic arsenicals may have limited nephrotoxicity, but it is difficult to judge the significance of these observation for humans exposed to organic arsenicals.

Dermal/Ocular Effects. Perhaps the single most common and characteristic sign of exposure to inorganic arsenic is a triad of dermatological manifestations, including hyperkeratinization of the skin (especially on the palms and soles), formation of multiple hyperkeratinized corns or warts, and hyperpigmentation of the skin with interspersed spots of hypopigmentation. One or more of these effects have been noted in numerous studies of intermediate or chronic oral exposure to inorganic arsenic (e.g., Borgono and Greiber 1972; Cebrian et al. 1983; Chakraborty and Saha 1987; Mazumder et al. 1988; Nagai et al. 1956; Tay and Seah 1975; Tseng et al. 1968; Zaldivar 1977), and similar effects have also been noted only rarely in workers exposed to inorganic arsenic primarily by the inhalation route (Perry et al. 1948). These effects appear to be of relatively little health significance in their own right, although a small fraction of the hyperkeratinized corns may ultimately progress to squamous cell carcinoma of the skin (see below).

Since these skin lesions appear to be the earliest observable sign of chronic exposure, this end point is considered to be the most appropriate for derivation of a chronic MRL. Oral exposure data from studies in humans (Cebrian et al. 1983; Hindmarsh et al. 1977; Southwick et al. 1981; Tseng 1977; Tseng et al. 1968) identify a chronic average daily intake of about 0.01–0.02 mg As/kg/day as the approximate LOAEL for skin lesions, and indicate the NOAEL is between 0.0004 and 0.0009 mg As/kg/day. The NOAEL of 0.0008 mg As/kg/day identified by Tseng et al. (1968) and Tseng (1977) has been selected as the most appropriate basis for calculation of a chronic oral MRL for inorganic arsenic because of the large number of people in the study. However, because the population in the no-effect group were relatively young (only 38% older than 20 and 17% older than 40), there is some chance that dermal effects might not have had time to occur, and might become manifest as the population ages. For this reason, the MRL is derived from the NOAEL by an uncertainty factor of 3. Chronic inhalation data suggest that exposure of workers to about 0.1–1.0 mg As/m^3 may lead to

hyperkeratinization and hyperpigmentation (Perry et al. 1948), but in the absence of other studies to support this, and without identification of a reliable NOAEL, these data are not considered sufficient for derivation of a chronic inhalation MRL.

Direct dermal contact with inorganic arsenicals may cause irritation and contact dermatitis. Usually the effects are mild (erythema and swelling) but may progress to papules, vesicles, or necrotic lesions in extreme cases (Holmqvist 1951). These conditions tend to heal without treatment if exposure ceases. Effects of this sort have only been observed in workplace environments where there are high levels of arsenic dusts (Holmqvist 1951; Pinto and McGill 1953), and have not been noted in people exposed to arsenic in water or soil (presumably because the concentrations of arsenic that contact the skin from water or soil are too low to cause significant irritation).

Little information was located on dermal or ocular effects of organic arsenicals. Workers exposed to arsanilic acid did not complain of dermal problems (Watrous and McCaughey 1945), but no direct examination or comparison of dermal appearance of the workers with a control group was performed. Rats exposed to very high concentrations of DMA developed erythema on the ears and feet along with encrustations around the eyes (Stevens et al. 1979). These effects were presumably due to direct irritation from dermal contact, suggesting that at least some of the organic arsenicals may be able to cause contact dermatitis. However, these data are too limited to draw firm conclusions.

Immunological Effects. No studies were located on immune effects in humans after oral exposure to inorganic arsenicals, but workers exposed to arsenic dusts in air did not have altered levels of antibodies in their blood (Bencko et al. 1988). Mice exposed to arsenate in drinking water did not display any signs of immunotoxicity (Kerkvliet et al. 1980), and mice given intratracheal doses of sodium arsenite had decreased humoral responsiveness to antigens but no measurable decrease in resistance to bacterial or cellular pathogens (Sikorski et al. 1989). Repeated dermal contact with arsenic dusts in the workplace may lead to dermal sensitization (Holmqvist 1951), but sensitization appears to be very rare in the general population (Wahlberg and Boman 1986). Overall, these data suggest that the immune system is probably not a major target of arsenic, but the data are too sparse to draw firm conclusions.

No studies were located regarding immunological effects in humans or animals after exposure to organic arsenicals.

Neurological Effects. Signs of peripheral and/or central neuropathy are common in humans exposed to inorganic arsenicals by the oral route, and have also been observed in some workers exposed by the inhalation route. Acute, high dose exposure can lead to encephalopathy, with clinical signs such as confusion, hallucinations, impaired memory, and emotional lability (Beckett et al. 1986; Danan et al. 1984; Morton and Caron 1989). In fatal or near fatal cases, this may progress to seizures and coma (Armstrong et al. 1984; Fincher and Koerker 1987), while lower-level exposure can lead to significant peripheral neuropathy (e.g., Feldman et al. 1979; Huang et al. 1985; Landau et al. 1977; Mizuta et al. 1956; Silver and Wainman 1952). This neuropathy is usually first detected as a numbness in the hands and feet, but may progress to a painful "pins and needles" sensation (Franzblau and Lilis 1989; Jenkins 1966; LeQuesne and McLeod 1977). Both sensory and motor neurons are affected, with distal axon degeneration and demyelination (Goebel et al. 1990; Hindmarsh and McCurdy 1986). More advanced symptoms include weakness, loss of reflexes, and wrist-drop or ankle-drop (Chhuttani et al. 1967; Heyman et al. 1956). These effects may diminish after exposure ceases, but recovery is slow and usually is not complete (Beckett et al. 1986; Fincher and Koerker 1987; LeQuesne and McLeod 1977; Morton and Caron 1989; Murphy et al. 1981).

No studies were located regarding neurological effects in humans after exposure to organic arsenicals, but pigs given repeated oral doses of roxarsone developed muscle tremor, paralysis, and seizures (Edmonds and Baker 1986; Rice et al. 1985), along with a degeneration of myelinated axons in the spinal cord (Kennedy et al. 1986). These findings indicate that neurotoxicity may be an effect of concern for organic as well as inorganic arsenicals, but it is not possible to estimate human NOAEL or LOAEL values from the existing data.

Developmental Effects. There are several epidemiological studies that have reported an association between exposure to inorganic arsenic and increased risk of adverse developmental effects (congenital malformations, low birth weight, spontaneous abortion), both by the inhalation route (Nordstrom et al. 1978a, 1978b, 1979a, 1979b) and the oral route (Aschengrau et al. 1989; Zierler et al. 1988). However, in all of these studies the populations were exposed to a number of other chemicals and risk factors which may have contributed to the observed effects, and these studies provide only suggestive evidence that arsenic was a causative agent. Studies in animals, however, do support the view that arsenic is a developmental toxicant, causing reduced birth weight, a variety of fetal malformations (both skeletal and soft tissue), and increased fetal mortality. These effects have been noted following inhalation exposure of mice (Nagymajtenyi et al. 1985), oral exposure of mice and hamsters (Baxley et al. 1981; Hood and Harrison 1982; Hood et al. 1978), and intraperitoneal or intravenous injection of rats, mice, and hamsters (Beaudoin 1974; Carpenter 1987; Ferm and Carpenter 1968; Ferm et al. 1971; Hanlon and Ferm 1986c; Hood and Bishop 1972; Mason et al. 1989; Willhite 1981). However, in all cases the doses required to cause these effects were high (2–20 mg As/kg/day by injection, 20–70 mg As/kg/day by the oral route, 20 mg As/m^3 by inhalation), and often resulted in significant maternal toxicity or even lethality (Baxley et al. 1981; Hood and Bishop 1972; Hood and Harrison 1982). These data suggest that although inorganic arsenic is a developmental toxicant, the developing fetus is not especially susceptible, and teratogenicity or fetotoxicity are unlikely to be of concern except at doses that are also toxic to the pregnant female.

No studies were located regarding developmental effects in humans after exposure to organic arsenicals. Oral exposure of mice and rats to DMA during gestation resulted in minor fetal effects (malformed palates, decreased weight gain, delayed ossification), although doses that were maternally toxic also caused increased fetal death (Rogers et al. 1981). Intraperitoneal injection of hamsters with MMA or DMA caused no obvious teratogenic or fetotoxic effects at a dose of 54 mg As/kg (Willhite 1981), although very high doses (420–460 mg As/kg/day) caused stunted growth, malformations, and both fetal and maternal deaths (Hood et al. 1982). These studies suggest that the organic arsenicals are significantly less fetotoxic than the inorganic arsenicals, and are not likely to cause developmental effects in humans except at very high exposure levels.

Reproductive Effects. Only limited information exists on the reproductive effects of inorganic arsenic. No human studies were located, and only one study (Schroeder and Mitchner 1971, a three-generation oral exposure study in mice) has been performed in animals. This study revealed no significant effects on reproductive success, although a slight trend toward decreased pups per litter and a slightly altered male:female ratio were noted. In the absence of additional data, no firm conclusions can be drawn, but this study does not indicate that inorganic arsenic is a potent reproductive toxicant.

Data are also very limited on the reproductive effects of organic arsenicals. No studies were located on effects in humans, but oral exposure of male mice to MMA resulted in a clear decrease in the number of females producing litters (Prukop and Savage 1986). This suggests that MMA might interfere with sperm production, but the effects could also be due to reduced mating as a consequence of illness from nonreproductive effects. Thus, in the absence of additional information, the reproductive toxicity of organic arsenicals cannot be evaluated.

Genotoxic Effects. There have been a large number of studies of the genotoxic effects of arsenic. Tables 2-6 and 2-7 summarize a number of reports on the in vivo and in vitro genotoxicity of inorganic arsenicals, respectively. The results are mixed, but in general it appears that the inorganic arsenicals are either inactive or weak mutagens (Jacobson-Kram and Montalbano 1985), but are able to produce chromosomal effects (aberrations, sister chromatid exchange) in most systems. Studies of humans have detected higher-than-average incidence of chromosomal aberrations in peripheral lymphocytes, both after inhalation exposure (Beckman et al. 1977; Nordenson et al. 1978) and oral exposure (Burgdorf et al. 1977; Nordenson et al. 1979). These studies must be interpreted with caution, since in most cases there were only a small number of subjects and a number of other chemical exposures were possible (EPA 1984a). However, the in vivo findings are strongly supported by in vitro studies using eukaryotic cells (e.g., Lee et al. 1985; Nakamuro and Sayato 1981; Zanzoni and Jung 1980; see Table 2-7).

The genotoxicity of the organic arsenicals has not been as thoroughly studied, but several tests indicate that DMA and roxarsone may be able to cause mutations and DNA strand breaks (see Table 2-8). Without additional data, it is difficult to judge whether these effects are of human health significance.

Cancer. There is clear evidence from studies in humans that exposure to inorganic arsenic may increase the risk of cancer. In workers exposed by the inhalation route, the predominant carcinogenic effect is increased risk of lung cancer (e.g., Axelson et al. 1978; Enterline and Marsh 1982; Lee-Feldstein 1986; Pinto et al. 1977; Welch et al. 1982), although a few reports have noted increased incidence of tumors at other sites (e.g., Lee-Feldstein 1983; Pinto et al. 1977; Tsuda et al. 1987). Based on the risk of lung cancer, EPA has assigned inorganic arsenic to Group A (known human carcinogen) by the inhalation route (IRIS 1992). This is supported by the U.S. Public Health Service, which has also classified arsenic as a known human carcinogen (NTP 1989a). In general, most researchers observe that risk increases as a function of exposure level and duration (Axelson et al. 1978; Jarup et al. 1989; Lee-Feldstein 1983; Mabuchi et al. 1979; Pinto et al. 1978). Most cases are seen in workers with chronic exposures, although several studies suggest that even short (1 year) exposures may also increase risk (Lee-Feldstein 1986; Sobel et al. 1988). Computer modeling of available epidemiological data suggests that arsenic acts mainly as a promoter, increasing lung cancer by increasing the rate of a late stage in the carcinogenic sequence, although it may also act at an early stage (Brown and Chu 1983c; Enterline and Marsh 1982; Mazumdar et al. 1989).

When exposure occurs by the oral route, the main carcinogenic effect is increased risk of skin cancer. This conclusion is based on a number of epidemiological studies of populations exposed to elevated levels of arsenic in drinking water (e.g., Tseng et al. 1968; Wu et al. 1989; Zaldivar 1974), and on numerous case reports of people exposed to Fowler's solution (Bickley and Papa 1989; Piontek et al. 1989; Sommers and McManus 1953). Based on these findings, the EPA has placed inorganic arsenic in Group A (known human carcinogen) for exposure by the oral route. In addition to skin cancer, there are a number of case reports (Kasper et al. 1984; Lander et al. 1975; Regelson et al. 1968; Roth 1957; Sommers and McManus 1953) and epidemiological studies (Chen et al. 1985, 1986, 1988a, 1988b, 1988c; Chiang et al. 1988; Wu et al. 1989) that indicate ingestion of arsenic also increases the risk of internal tumors (mainly of liver, bladder, kidney, and lung).

As discussed previously (see Section 2.2.2.8), EPA has calculated an oral cancer slope factor for inorganic arsenic based on the dose-response data obtained in Taiwan by Tseng et al. (1968). This slope factor was calculated using a model that assumes the dose-response curve is linear at low doses. Recently, it has been suggested that this slope factor may over-estimate cancer risks at low dose, since low doses may be largely "detoxified" by in vivo methylation, producing a nonlinear dose-response curve (Marcus and Rispin 1988). If so, this would be of

TABLE 2-6. Genotoxicity of Inorganic Arsenic In Vivo

Valence	Exposure route	Species (test system)	End point	Results	Reference
As(+3)	Inhalation	Human (lymphocytes)	Chromosomal aberrations	-	Beckman et al. 1977
As(+3)	Inhalation	Human (lymphocytes)	Chromosomal aberrations	+	Nordenson et al. 1978
No data	Oral	Human (lymphocytes)	Chromosomal aberrations	-	Vig et al. 1984
No data	Oral	Human (lymphocytes)	Sister chromatid exchange	-	Vig et al. 1984
As(+3)	Oral	Human (lymphocytes)	Chromosomal aberrations	-	Burgdorf et al. 1977
As(+3)	Oral	Human (lymphocytes)	Sister chromatid exchange	-	Nordenson et al. 1979
As(+3)	Oral	Human (lymphocytes)	Sister chromatid exchange	+	Burgdorf et al. 1977
As(+3)	Intraperitoneal	Mouse (bone marrow cells)	Chromosomal breaks, exchanges	-	Poma et al. 1981
As(+3)	Intraperitoneal	Mouse (bone marrow cells)	Micronuclei	+	DeKnudt et al. 1986
As(+3)	Intraperitoneal	Mouse (spermatogonia)	Spermatogonia	-	Poma et al. 1981
As(+3)	Intraperitoneal	Mouse (spermatogonia)	Sperm morphology	-	DeKnudt et al. 1986
As(+3)	Intraperitoneal	Mouse (spermatogenesis)	Dominant lethal mutations	-	DeKnudt et al. 1986
As(+3)	Oral	Mouse (bone marrow cells)	Chromosomal breaks, exchanges	-	Poma et al. 1987
As(+3)	Oral	Mouse (spermatogonia)	Chromosomal aberrations	-	Poma et al. 1987
As(+3)	Inhalation	Mouse (fetal liver)	Chromosomal aberrations	(+)	Nagymajtenyi et al. 1985
As(+5)	Oral	Rat (bone marrow cells)	Chromosomal aberrations	+	Datta et al. 1986

- = negative result; + = positive result; (+) = weakly positive result

TABLE 2-7. Genotoxicity of Inorganic Arsenic In Vitro

Valence	Species (test system)	End point	Results: With activation	Results: Without activation	Reference
	Prokaryotic organisms:				
As(+3)	Escherichia coli	Reverse mutation	No data	+	Nishioka 1975
	E. coli (6 strains)	Reverse mutation	No data	-	Rossman et al. 1980
	Salmonella typhimurium	Gene mutation	No data	-	Lofroth and Ames 1978
	Photobacterium fischeri	Gene mutation	No data	-	Ulitzur and Barak 1988
As(+5)	S. typhimurium	Gene mutation	No data	-	Lofroth and Ames 1978
	P. fischeri	Gene mutation	No data	+	Ulitzur and Barak 1988
	Eukaryotic organisms:				
	Fungi:				
As(+3)	Saccharomyces cerevisiae	Gene mutation	No data	-	Singh 1983
	Mammalian cells:				
As(+3)	Syrian hamster embryo cells	Morphological transformation	No data	+	Lee et al. 1985
	Syrian hamster embryo cells	Morphological transformation	No data	+	Casto et al. 1979
	Syrian hamster embryo cells	Gene mutation	No data	-	Lee et al. 1985
	Syrian hamster embryo cells	Sister chromatid exchange	No data	+	Lee et al. 1985
	Syrian hamster embryo cells	Chromosomal aberration	No data	+	Lee et al. 1985
	Chinese hamster V79 cells	Gene mutation	No data	-	Rossman et al. 1980
	Mouse lymphoma cells	Enhanced viral forward mutation	No data	(+)	Oberly et al. 1982
	Human fibroblasts	DNA repair inhibition	No data	+	Okui and Fujiwara 1986
	Human leukocytes	Chromosomal aberrations	No data	+	Nakamuro and Sayato 1981
	Human lymphocytes	Chromosomal aberrations	No data	+	Beckman and Nordenson 1986
	Human lymphocytes	Chromosomal aberrations	No data	+	Sweins 1983

TABLE 2-7 (Continued)

Valence	Species (test system)	End point	Results		Reference
			With activation	Without activation	
As(+5)	Syrian hamster embryo cells	Morphological transformation	No data	+	Lee et al. 1985
	Syrian hamster embryo cells	Morphological transformation	No data	+	DiPaolo and Casto 1979
	Syrian hamster embryo cells	Gene mutation	No data	-	Lee et al. 1985
	Syrian hamster embyro cells	Sister chromatid exchange	No data	+	Lee et al. 1985
	Syrian hamster embryo cells	Chromosomal aberrations	No data	+	Lee et al. 1985
	Mouse lymphoma cells	Gene mutation	No data	-	Amacher and Paillet 1980
	Human leukocyte	Chromosomal aberrations	No data	(+)	Nakamuro and Sayato 1981
	Human fibroblasts	DNA repair inhibition	No data	-	Okui and Fujiwara 1986
	Human peripheral lymphocytes	Sister chromatid exchange	No data	+	Zanzoni and Jung 1980

+ = positive result; - = negative result; (+) = weakly positive result

TABLE 2-8. Genotoxicity of Organic Arsenic

Chemical form	Species (test system)	End point	Results: With activation	Results: Without activation	Reference
	Prokaryotic organims (in vitro):				
Dimethylarsenic acid	Escherichia coli	Gene mutation	No data	+	Yamanaka et al. 1989b
Roxarsone	Salmonella typhimurium	Gene mutation	-	-	NTP 1989b
	Eukaryotic organisms (in vitro):				
Roxarsone	Mouse lymphoma (L5178Y) cells	Trifluorothymidine resistance	No data	+	NTP 1989b
Roxarsone	Drosophila melanogaster	Sex linked recessive mutations	No data	-	NTP 1989b
	Eukaryotic organisms (in vivo):				
Dimethylarsenic acid	Mouse (oral exposure)	DNA strand breaks in tissues	Not applicable	+	Yamanaka et al. 1989a

+ = positive result; - = negative result

considerable importance in estimating the cancer risk to people exposed to low levels of arsenic in water or soil. EPA has carefully considered this issue, and has concluded that while the current slope factor might overestimate low dose risk, at present the toxicokinetic data on human methylation rate and capacity and the toxicity data on the relative carcinogenic risk from methyl derivatives are too limited to permit any sort of quantitative adjustment to the slope factor (EPA 1988e).

The biochemical mechanism of arsenic-induced carcinogenicity is not known. As discussed previously, arsenic does not appear to damage DNA by a direct mechanism, but several studies support the concept that arsenic inhibits one or more of the enzymes involved in DNA replication or repair (Li and Rossman 1989; Nordberg and Anderson 1981; Okui and Fujiwara 1986; Rossman 1981). Another possible mechanism of arsenic-induced carcinogenicity is incorporation of arsenate into DNA in place of phosphate (Nordberg and Anderson 1981). This concept is consistent with observations that arsenate must be present during DNA synthesis in order to be effective, and would explain why arsenic is clastogenic (the arsenate-phosphate bond would be weaker than the normal phosphodiester) but does not cause gene mutations (Jacobson-Kram and Montalbano 1985).

Beneficial Effects. There are several studies in animals which suggest that low levels of arsenic in the diet are beneficial or essential. Rats fed a low-arsenic diet (<0.05 ppm of arsenic in food, corresponding to about 0.0025 mg As/kg/day) did not gain weight normally (Schwartz 1977; Uthus et al. 1983), and arsenic deprivation has been noted to decrease the growth of offspring from rats, goats, and minipigs (Anke et al. 1976, 1978; Uthus et al. 1983). Decreased reproductive success and increased postnatal mortality has also been noted in goats, minipigs, and rats maintained on low-arsenic diets (Anke et al. 1976, 1978; Uthus et al. 1983). No specific biochemical mechanism is known by which arsenic could be exerting a beneficial effect, but Nielsen et al. (1980) and Uthus et al. (1983) have proposed that arsenic plays a role in arginine and/or zinc metabolism.

While these observations suggest that low levels of arsenic may be essential or beneficial to animals, several researchers consider the weight of evidence inadequate to conclude this with certainty (Hindmarsh and McCurdy 1986; Solomons 1984). EPA (1988e) performed a detailed review of the evidence, and concluded that essentiality, although not rigorously established, is plausible.

If arsenic is essential or beneficial to animals, then it could be important to humans as well. If so, the daily requirement for humans probably lies somewhere between 10 and 50 µg/day (0.0001–0.0007 mg As/kg/day) (EPA 1988e; NAS 1977b). This level of arsenic intake is usually provided in a normal diet (about 50 µg/day; see Section 5.5), and no cases of arsenic deficiency in humans have ever been reported.

2.5 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule or cell that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time biologic samples can

be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to arsenic are discussed in Section 2.5.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are often not substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by arsenic are discussed in Section 2.5.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, biologically effective dose, or target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.7, "Populations That Are Unusually Susceptible."

2.5.1 Biomarkers Used to Identify or Quantify Exposure to Arsenic

Arsenic levels in blood, urine, hair, and nails have all been investigated and used as biological indicators of exposure to arsenic. Since arsenic is cleared from blood within a few hours (Tam et al. 1979b; Vahter 1983), measurements of blood arsenic reflect exposures only within the very recent past. Typical values in nonexposed individuals are less than 1 μg/L (Heydorn 1970; Hindmarsh and McCurdy 1986; Valentine et al. 1979). Consumption of medicines containing arsenic is associated with blood values of 100–250 μg/L, while blood levels in acutely toxic and fatal cases may be 1,000 μg/L or higher (Driesback 1980). However, blood levels do not appear to be reliable indicators of chronic exposure to low levels of arsenic. For example, there was no correlation between the level of arsenic in blood of residents and the level of arsenic in drinking water in several U.S. communities where water levels ranged from about 6 to 125 μg/L (Valentine et al. (1979, 1981). Consequently, measurement of blood arsenic is not generally considered to be a reliable means of monitoring human populations for arsenic exposure.

As discussed in Section 2.3.4, most arsenic that is absorbed from the lungs or the gastrointestinal tract is excreted in the urine, mainly within 1–2 days. For this reason, measurement of urinary arsenic levels is generally accepted as the most reliable indicator of recent arsenic exposure, and this approach has proved useful in identifying above-average exposures in populations living near industrial point sources of arsenic (e.g., Milham and Strong 1974; Polissar et al. 1990). By the inhalation route, several researchers have found there is a good quantitative correlation between the concentration of arsenic in workplace air (C_{air}, μg/m^3) and the concentration in the urine (C_{urine}, μg/L) of exposed workers. For example, Pinto et al. (1976) found a linear relationship for exposures ranging up to 150 μg/m^3, given by the following equation:

$$C_{air} = 0.3\ C_{urine}$$

More recently, Enterline et al. (1987a) reinvestigated this relationship over a wider range of exposures (up to 3,500 μg/m^3), and found that the curve tended to be concave upward, as given by the following equation:

$$C_{air} = 0.0064\ (C_{urine})^{1.94}$$

This indicates that at higher exposure levels a higher fraction of the dose is excreted in urine, although the toxicokinetic basis for this is not certain. A similar quantitative relation between ingested arsenic and urinary excretion levels has not been reported, but numerous studies have used above-average urinary levels (i.e., higher than about 100 μg/L) as evidence of recent arsenic ingestion (e.g., Borgono et al. 1980; Fincher and Koerker 1987; Franzblau and Lilis 1989; Goldsmith and From 1986; Kyle and Pease 1965; Valentine et al. 1981).

An important limitation to the use of total urinary arsenic as a biomarker of exposure is that arsenobetaine is excreted (unmetabolized) in urine after ingestion of certain seafoods (Brown et al. 1990; Kalman 1987; Tam et al. 1982). Since "fish arsenic" is essentially nontoxic, analytical methods based on total urinary arsenic content may overestimate exposures to arsenic species that are of health concern. As discussed in Section 6.1, there are adequate methods for distinguishing arsenobetaine from other forms of arsenic in urine (inorganic, MMA, DMA), although these are not convenient to use as a routine screening method.

Arsenic tends to accumulate in hair and nails, and measurement of arsenic levels in these tissues may be a useful indicator of past exposures. Normal levels in hair and nails are 1.0 ppm or less (Choucair and Ajax 1988; Franzblau and Lilis 1989). These values may increase from several-fold to over 100-fold following arsenic exposure (Agahian et al. 1990; Bencko et al. 1986; Landau et al. 1977; Milham and Strong 1974; Southwick et al. 1981; Valentine et al. 1979; Yamauchi et al. 1989) and remain elevated for 6–12 months (Choucair and Ajax 1988). Minimum exposure levels which produce measurable increases in arsenic levels in hair and nails have not been precisely defined. For hair, ingestion of 50–120 ppb of arsenic in drinking water produced only a marginal effect, but a clear increase was noted at 393 ppb (Valentine et al. 1979). Inhalation exposure of workers to about 0.6 $\mu g/m^3$ of arsenic in air significantly increased average levels in nails (Agahian et al. 1990), although there was wide variation between individuals.

Analysis of hair may yield misleading results due to the presence of arsenic adsorbed to the external surface, but this can be minimized by collecting samples from close to the scalp or from unexposed areas, and by washing the hair before analysis (e.g., Paschal et al. 1989). Similarly, extensive washing of nails is required to remove exogenous contamination (Agahian et al. 1990).

2.5.2 Biomarkers Used to Characterize Effects Caused by Arsenic

As discussed in Section 2.2, the characteristic pattern of skin changes caused by arsenic (hyperkeratinization, hyperpigmentation) is probably the most sensitive and diagnostic clinical indicator of chronic exposure to arsenic. However, no means has been developed for detecting these effects except by routine dermatological examination.

Peripheral neuropathy is another characteristic effect of arsenic exposure, and several researchers have investigated decreased nerve conduction velocity or amplitude as a biomarker for peripheral neuropathy. While effects can usually be detected in individuals with clinical signs of neuropathy (e.g., Goebel et al. 1990; Jenkins 1966; LeQuesne and McLeod 1977; Morton and Caron 1989; Murphy et al. 1981), effects are only marginal (Hindmarsh et al. 1977; Landau et al. 1977; Valentine et al. 1981) or undetectable (Kreiss et al. 1983; Southwick et al. 1981) in exposed populations without obvious clinical signs of toxicity. This indicates that this approach is probably not sufficiently sensitive to detect neurological effects earlier than by standard neurological examination (Hindmarsh and McCurdy 1986). Also, decreases in nerve conduction velocity or amplitude are not specific for arsenic-induced neuropathy.

Arsenic is known to affect the activity of a number of enzymes, and some of these may have potential as biomarkers of effect. Most promising is the spectrum of effects which arsenic causes on the group of enzymes responsible for heme synthesis and degradation, including inhibition of coproporphyrinogen oxidase and heme

synthetase (Woods and Fowler 1978; Woods and Southern 1989) and activation of heme oxygenase (Sardana et al. 1981). It has been shown in animals that these arsenic-induced enzymic changes result in increased urinary levels of uroporphyrin, coproporphyrin, and bilirubin (Albores et al. 1989; Woods and Fowler 1978), but it is not known if these effects can be detected in the urine of arsenic-exposed humans. If so, increased urinary levels of these heme-related compounds could serve as a biomarker of exposure. However, it is known that numerous other toxic metals also have similar effects on heme metabolism (Albores et al. 1989; Sardana et al. 1981; Woods and Southern 1989), so it is likely these effects would not be specific for arsenic.

2.6 INTERACTIONS WITH OTHER CHEMICALS

A number of researchers have found that arsenic compounds tend to reduce the effects of selenium (Hill 1975; Howell and Hill 1978; Levander 1977; Schrauzer 1987). Conversely, selenium can decrease the effects of arsenic, including clastogenicity (Beckman and Nordenson 1986; Sweins 1983), cytotoxicity (Babich et al. 1989; Rossner et al. 1977), and teratogenicity (Holmberg and Ferm 1969). The mechanism of this mutual inhibition of effects is not known, but may be related to formation of a complex that is excreted more rapidly than either arsenic or selenium alone (Cikrt et al. 1988; Hill 1975; Levander 1977). There is little direct evidence that variations in selenium exposure in humans lead to significant increases or decreases in arsenic toxicity, although workers who developed lung cancer in a copper smelter had lower tissue levels of selenium than workers who did not develop lung tumors (Gerhardsson et al. 1985, 1988). This suggests that selenium deficiency could significantly increase the risk of lung cancer following inhalation exposure to arsenic, but it is difficult to distinguish cause from effect in such a study.

The interaction between cigarette smoking, inhalation of arsenic, and the risk of lung cancer has not been extensively investigated. Smoking appeared to increase lung cancer risk synergistically (multiplicatively) in one study of smelter workers (Pershagen et al. 1981), although the data are not adequate to exclude a simple additive interaction (Thomas and Whittemore 1988). Suggestive evidence of a positive interaction between arsenic and benzo(a)pyrene has also been noted for induction of lung adenocarcinomas in hamsters (Pershagen et al. 1984a).

Interactions between arsenic and other metals have been investigated, but no clear evidence for toxicologically significant effects has emerged. For example, studies of rats exposed to arsenic, lead, and cadmium, alone or in combination, revealed mainly additive or sub-additive effects on body weight, hematological parameters, and enzymes of heme synthesis (Mahaffey and Fowler 1977; Mahaffey et al. 1981). Similarly, studies of the tissue levels of arsenic in rats fed arsenic with or without lead or cadmium revealed only limited evidence of any toxicokinetic interactions (Mahaffey et al. 1981). These data do not suggest that arsenic toxicity is likely to be significantly influenced by concomitant exposure to other metals.

Since methylation of arsenic is a detoxification mechanism, it is possible that chemicals which interfere with the methylation process could increase toxicity. This is supported by studies in animals in which reagents that inhibit methylation enzymes (e.g., periodate-oxidized adenosine) caused an increase in tissue levels of inorganic arsenic (Marafante et al. 1985; Marafante and Vahter 1986). Similarly, cellular glutathione levels appear to play a role in the methylation process, and treatment with reagents (e.g., phorone) that decrease glutathione levels increases arsenic toxicity (Buchet and Lauwerys 1987). It is not known if chemicals likely to be encountered in the environment cause significant effects on the methylating capacity of humans.

2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to arsenic than will most persons exposed to the same level of arsenic in the environment. Reasons include genetic make-up, developmental stage, health and nutritional status, and chemical exposure history. These parameters result in decreased function of the detoxification and excretory processes (mainly hepatic and renal) or the pre-existing compromised function of target organs. For these reasons we expect the elderly with declining organ function and the youngest of the population with immature and developing organs will generally be more vulnerable to toxic substances than healthy adults. Populations who are at greater risk due to their unusually high exposure are discussed in Section 5.6, "Populations With Potentially High Exposure."

No studies were located regarding unusual susceptibility of any human subpopulation to arsenic. However, since the degree of arsenic toxicity may be influenced by the rate and extent of its methylation in the liver (see Section 2.3.3), it seems likely that some members of the population might be especially susceptible because of lower than normal methylating capacity. Reduced hepatic methylation could result from dietary deficiency of methyl donors such as choline or methionine (Buchet and Lauwerys 1987; Vahter and Marafante 1987), although this is unlikely to be a concern for most people. While there is some evidence that methylation capacity does vary among individuals (e.g., Buchet et al. 1981a; Foa et al. 1984; Tam et al. 1979b), the basis of this variation and its impact on human susceptibility have not been established. Liver disease does not appear to decrease methylation capacity in humans, at least at low levels of arsenic exposure (Buchet et al. 1982; Geubel et al. 1988).

2.8 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to arsenic. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to arsenic. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

2.8.1 Reducing Peak Absorption Following Exposure

No data were located regarding the reduction of absorption after inhalation exposure to arsenic.

There are a number of methods for reducing absorption of arsenic following oral exposure. In cases of acute high dose exposure, the removal of arsenic from the gastrointestinal tract may be facilitated by gastric lavage, stomach intubation, induced emesis or use of cathartics (saline, sorbitol) within a few hours after ingestion (Aposhian and Aposhian 1989; ATSDR 1990; Campbell and Alvarez 1989; Driesback 1980; Ellenhorn and Barceloux 1988; EPA 1989e; Haddad and Winchester 1990; Stutz and Janusz 1988). However, the efficacy of several of these methods has been questioned by some authors, and in some cases, the treatments may be contraindicated. For example, vomiting and diarrhea often occur soon after ingesting arsenic, and therefore, use of an emetic or cathartic may not be necessary. Also, emesis should not be induced in obtunded, comatose, or convulsing patients (Campbell and Alvarez 1989; Ellenhorn and Barceloux 1988; EPA 1989e), and saline cathartics should be used with caution in patients with impaired renal function (Campbell and Alvarez 1989). Treatments of this sort are unlikely to be required following low-level exposures.

Another possible approach for reducing absorption following oral exposure is to administer substances which bind the arsenic in the gastrointestinal tract. For example, activated charcoal is sometimes used for this purpose (Campbell and Alvarez 1989; EPA 1989e; Stutz and Janusz 1988), although the effectiveness of this treatment is not well established. Because pentavalent arsenic is a phosphate analogue, administration of phosphate-binding

substance such as aluminum hydroxide might possible be useful, but this has not been investigated. Sulfhydryl compounds might be given to bind trivalent arsenic, but is seems unlikely that these would be effective under the acid conditions in the stomach, and it is not clear that such complexes would have reduced gastrointestinal absorption.

Following dermal/ocular exposure to arsenic, several measures can be taken to minimize absorption. All contaminated clothing should be removed, and contacted skin should be immediately washed with soap and water. Eyes that have come in contact with arsenic should be flushed with copious amounts of clean water (EPA 1989e; Stutz and Janusz 1988).

2.8.2 Reducing Body Burden

Acute arsenic intoxication may require treatment with chelating agents such as dimercaprol (BAL) and D-penicillamine. Although body burden is not necessarily reduced, these chelators bind free arsenic and serve to reduce the body's pool of biologically active arsenic. Chelation therapy is most effective when instituted within a few hours after exposure, and efficacy decreases as time after exposure increases (ATSDR 1990).

In general, chelating agents should be used with caution since they may have serious side effects such as pain, fever, hypotension, and nephrotoxicity (Ellenhorn and Barceloux 1988). Some water-soluble and less toxic analogues of BAL such as dimercaptosuccinic acid (DMSA), dimercaptopropyl phthalamadic acid (DMPA), and dimercaptopropane sulfonic acid (DMPS) are currently under investigation and may prove to be promising treatments for arsenic poisoning (Aposhian and Aposhian 1989; ATSDR 1990). N-acetylcysteine has been used in animals to chelate arsenic (Haddad and Winchester 1990), and a human case study reported N-acetylcysteine to be successful in treating a case of arsenic poisoning which was not responding well to BAL treatment (Martin et al. 1990).

As discussed in Section 2.3.3, once arsenic has been absorbed into the blood stream, it undergoes methylation to yield MMA and DMA. These forms of arsenic are less toxic than inorganic arsenic and are cleared from the body by excretion in the urine. Therefore, if it were possible to enhance arsenic methylation, both body burden and toxicity of arsenic might be reduced. However, experimental evidence in animals and humans suggests that arsenic methylation is not enhanced to any significant degree by supplementation with methylation cofactors (Buchet et al. 1982; Buchet and Lauwerys 1987), presumably because it is enzyme level and not cofactor availability that is rate limiting in arsenic methylation.

2.8.3 Interfering with the Mechanism of Action for Toxic Effects

It is generally thought that trivalent arsenic exerts its toxic effects mainly by complexing with sulfhydryl groups in key enzymes within the body, thereby inhibiting critical functions such as gluconeogenesis and DNA repair (Aposhian and Aposhian 1989; Li and Rossman 1989). Therefore, administration of sulfhydryl-containing compounds soon after exposure could provide alternative target molecules for arsenic, and prevent inhibition of enzyme functions. In fact, many of the chelating agents discussed above (BAL, DMSA, DMPA, DMPS, N-acetylcysteine) contain sulfhydryl groups, and this may account for their efficacy.

The mechanism by which pentavalent arsenic acts is less certain. Since pentavalent arsenic is reduced in the body to the trivalent state, pentavalent arsenic may act in a similar manner as described above for trivalent arsenic. If this is the case, efforts to inhibit the reduction of pentavalent arsenic would decrease its toxicity. However, no methods are currently recognized for blocking this reduction. Pentavalent arsenic may also exert effects by acting as a phosphate analogue. As a phosphate analogue, pentavalent arsenic could potentially affect a number

of biological processes including ATP production, bone formation, and DNA synthesis. However, any effort to interfere in normal phosphate metabolism could produce serious side effects, and no method is known for selectively interfering with arsenate metabolism.

2.9 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of arsenic is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of arsenic.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce or eliminate the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

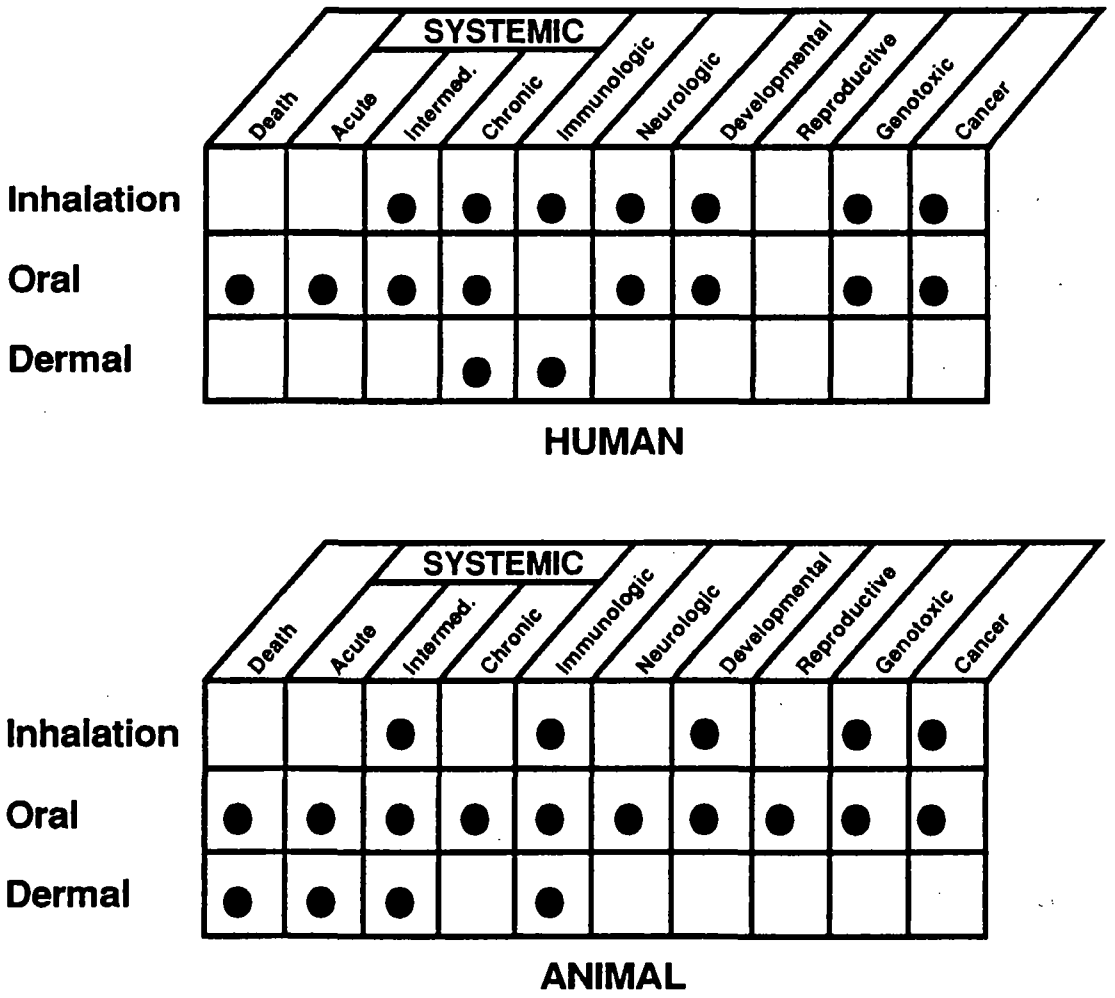
2.9.1 Existing Information on Health Effects of Arsenic

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to inorganic arsenic are summarized in Figure 2-5, and the corresponding information for organic arsenicals is shown in Figure 2-6. The purpose of these figures is to illustrate the existing information concerning the health effects of arsenic. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not imply anything about the quality of the study or studies. Gaps in this figure should not be interpreted as "data needs" information (i.e., data gaps that must necessarily be filled).

As shown in Figure 2-5, there is a substantial database on the toxicity of inorganic arsenicals, both in humans and in animals. The oral route has been most thoroughly investigated, and reports are available on most end points of concern following acute, intermediate, and chronic exposure. The inhalation route has also been studied extensively, mainly in humans, with special emphasis on lung cancer. A number of noncancer end points have also been studied following inhalation exposure, but information on these effects is less extensive. Limited information on the effects of dermal exposure is also available in both humans and animals, focusing mainly on direct irritancy and dermal sensitization reactions. The absence of studies on other effects of inorganic arsenic following dermal exposure is probably not a critical data need, since dermal uptake of inorganic arsenic appears to be sufficiently limited that other routes of exposure (oral or inhalation) would almost always be expected to be of greater concern.

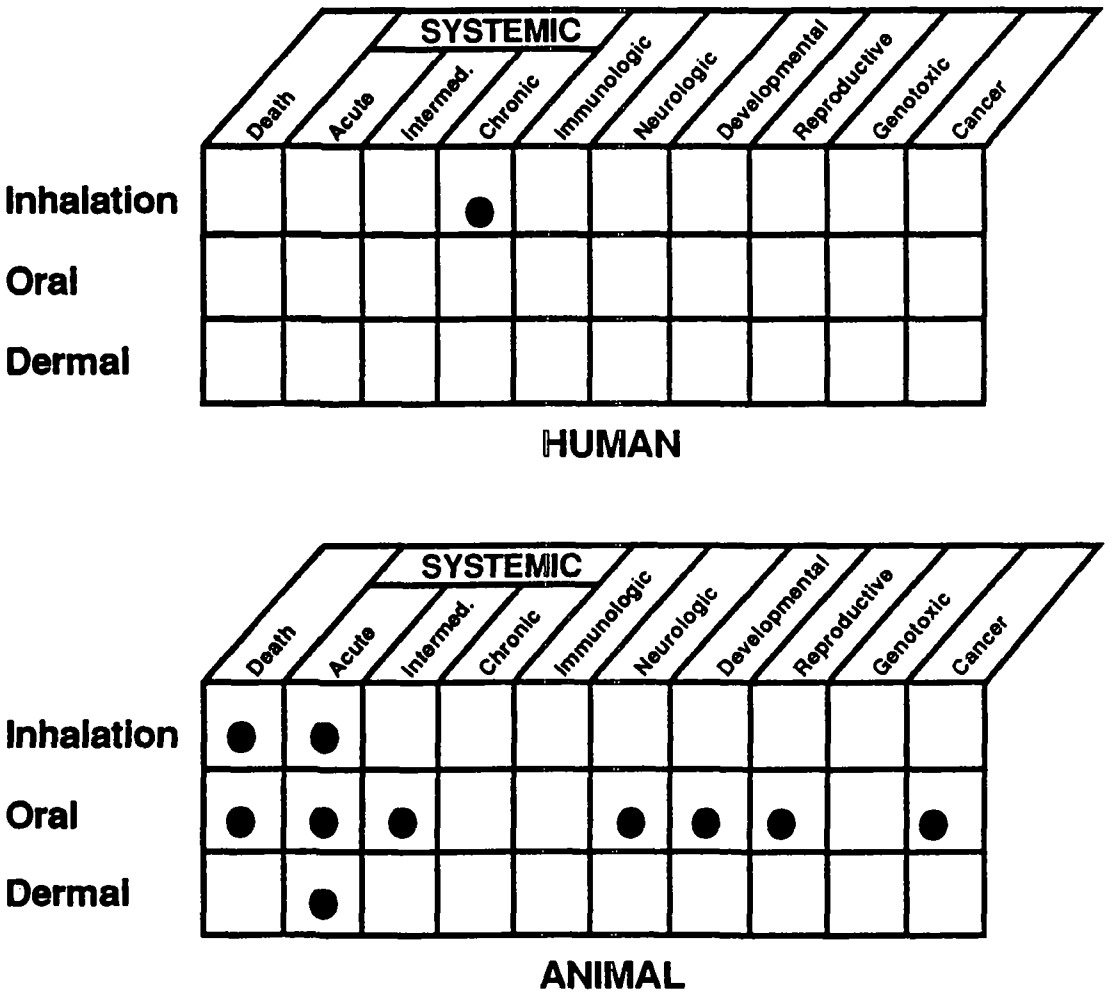
As shown in Figure 2-6, very little information is available on the effects of organic arsenic compounds in humans, although there are a number of studies in animals. These studies mainly involve the oral route since all of these compounds are nonvolatile solids, although a few acute inhalation studies have been performed. Limited information is available on acute dermal lethality and dermal irritancy of some organic arsenicals, but data are lacking on other effects of organic arsenicals following dermal exposure.

FIGURE 2-5. Existing Information on Health Effects of Inorganic Arsenic



● Existing Studies

FIGURE 2-6. Existing Information on Health Effects of Organic Arsenic



● Existing Studies

As discussed previously, in evaluating the adequacy of the database on arsenic, it is important to keep in mind that most studies in animals indicate that they are quantitatively less sensitive to arsenic than humans. For this reason, data from animal studies should be used to draw inferences about effects in humans only with caution.

2.9.2 Identification of Data Needs

Acute-Duration Exposure. There is only limited information on the effects of acute inhalation exposure to arsenic in humans, but the chief symptoms appear to be irritation of the respiratory and gastrointestinal tracts (Beckett et al. 1986; Bolla-Wilson and Bleecker 1987; Dunlap 1921; Ide and Bullough 1988; Morton and Caron 1989; Pinto and McGill 1953). Quantitative data are lacking, but effects generally appear to be mild even at high exposure levels. On this basis, it seems that risks of acute effects are probably low for inhalation exposures in the environment or near waste sites. Research to obtain a quantitative acute inhalation NOAEL value that could be used to derive an acute inhalation MRL would, therefore, be useful but not critical. There are numerous studies in humans on the acute oral toxicity of arsenic, and the main end points (gastrointestinal irritation, pancytopenia, hepatic and renal injury, neuropathy) are well characterized (Armstrong et al. 1984; Fincher and Koerker 1987). Many of these reports provide quantitative data on acute oral exposures, but most of these are related to fatal or near-fatal poisonings. Additional studies to define an acute oral NOAEL that could be used to derive an acute oral MRL in humans would be helpful, since humans might have brief oral exposures through ingestion of contaminated soil or water near waste sites. Although acute dermal exposure is unlikely to cause serious systemic injury, it can lead to contact dermatitis and skin sensitization (Holmqvist 1951; Pinto and McGill 1953). However, available data do not permit a quantitative estimate of the concentration of arsenic on the skin or in air, dust, soil, or water that causes these effects. Further research would be valuable to obtain a quantitative NOAEL for direct dermal effects, since humans may have dermal contact with contaminated soil or water near hazardous waste sites.

No information was located on the acute toxicity of organic arsenicals in humans. Acute lethality and systemic toxicity data exist for several compounds by both oral and inhalation exposure of animals, and these data suggest that the organic derivatives of arsenic may cause effects similar to the inorganic forms, but only at higher doses (Kaise et al. 1989; NTP 1989b; Rogers et al. 1981; Stevens et al. 1979). Even though these compounds appear to be less toxic than inorganic arsenic, additional studies (especially in humans) would be valuable, since acute oral, inhalation, or dermal exposures may occur during manufacture or use of agricultural organic arsenicals, or at waste sites where organic arsenicals have been deposited.

Intermediate-Duration Exposure. Intermediate-duration inhalation exposure of humans to arsenic appears to result in respiratory tract irritation (occasionally including perforation of the nasal septum) and mild gastrointestinal tract irritation (Ide and Bullough 1988). Quantitative data are too limited (only one study, of one individual) to derive an intermediate-duration inhalation MRL. Further studies to define the NOAEL for intermediate duration inhalation exposure of humans would be valuable, since humans could be exposed to arsenic-containing airborne dusts near smelters, chemical plants, or waste sites. Effects of intermediate-duration oral exposure are similar to those of acute oral exposure, but may also include development of vascular injury and a characteristic group of skin changes (Franzblau and Lilis 1989; Holland 1904; Mizuta et al. 1956; Wagner et al. 1979). Most studies indicate that these effects occur at doses of about 0.05 mg As/kg/day or higher, but the data do not provide a firm basis for identifying the intermediate-duration NOAEL. For this reason, no intermediate-duration oral MRL has been derived. Further studies to establish the NOAEL would be valuable, since humans could have intermediate-duration oral exposures to arsenic through ingestion of contaminated soil or water near smelters, chemical factories, or waste sites. Since dermal effects appear to be restricted to acute irritancy, intermediate-duration studies are probably not essential.

No information was located on the intermediate duration toxicity of organic arsenicals in humans. The intermediate-duration oral toxicities of roxarsone, MMA, and DMA have been investigated in animals (Edmonds and Baker 1986; Jaghabir et al. 1989; Kerr et al. 1963; NTP 1989b; Prukop and Savage 1986; Siewicki 1981), but data are lacking for any compound by the inhalation route. Further studies on the intermediate-duration oral, inhalation, and dermal toxicity of these compounds would be valuable, especially in humans, since people may be exposed to organic arsenicals during their manufacture or use, or from materials deposited in waste sites.

Chronic-Duration Exposure and Cancer. The target tissues of chronic duration exposure of humans to inorganic arsenic are the same as for intermediate-duration exposure for both the oral and inhalation routes. Effects of dermal exposure appear to be restricted to direct irritation of exposed surfaces. Quantitative data from one study identify an inhalation exposure level of about 0.1 mg As/m^3 as the LOAEL for skin changes (Perry et al. 1948), but because there are no additional supporting studies and a NOAEL is not clearly established, an inhalation MRL has not been derived. Additional studies in humans to define the chronic inhalation NOAEL for dermal or other effects would be valuable, since humans may be chronically exposed to arsenic dusts in air near smelters, chemical factories, or waste sites. Chronic oral exposure data from studies in humans indicate that the LOAEL for skin lesions and other effects is probably about 0.01–0.02 mg As/kg/day (10–20 µg As/kg/day), and that the NOAEL is probably between 0.0004 and 0.0009 mg As/kg/day (0.4–0.9 µg As/kg/day) (Cebrian et al. 1983; Hindmarsh et al. 1977; Southwick et al. 1981; Tseng 1977; Tseng et al. 1968). The NOAEL of 0.0008 mg As/kg/day from the study by Tseng et al. (1965) is appropriate for derivation of a chronic oral MRL, but an uncertainty factor of 3 was required to account for the fact that the population which constituted the no-effect group were relatively young (possibly decreasing the ability to detect dermal or other effects). For this reason, further epidemiological studies to provide additional support for the threshold dose for arsenic in humans would be valuable.

There are numerous studies in humans which establish that inorganic arsenic is a carcinogen by inhalation exposure (Enterline et al. 1987a, 1987b; Jarup et al. 1987; Lee-Feldstein 1986; Welch et al. 1982) and oral exposure (Chen et al. 1986, 1988b; Lander et al. 1975; Luchtrath 1983; Tseng et al. 1968, 1977; Zaldivar 1974; Zaldivar et al. 1981), and quantitative slope factors are available for each route. The carcinogenic effects of chronic dermal exposure to inorganic arsenicals has not been studied, but it does not seem likely that this is of concern, and studies on this are probably not essential. The mechanism of arsenic carcinogenicity is not known, although it appears that it may function mainly as a promoter. Further studies on the mechanism of arsenic toxicity would be particularly valuable, since this could improve our ability to evaluate human cancer risks from inhalation or oral exposures that might occur near waste sites. Also, mechanistic studies could help in the evaluation of cancer risks from organic derivatives (see below).

There is very little information on the chronic toxicity of organic arsenicals. One study of workers exposed to arsanilic acid did not identify any adverse effects, but no systematic, clinical, or toxicological examinations of exposed people were performed (Watrous and McCaughey 1945). A chronic study in rats and mice given roxarsone in the diet did not reveal any obvious clinical effects (Prier et al. 1963). These data suggest that the organic arsenicals have low chronic toxicity, but further studies (especially of humans exposed during manufacture or use of organic arsenicals) would be valuable in deriving estimates of safe exposure limits.

No information was located on carcinogenic effects of organic arsenicals in humans. The carcinogenic potential of roxarsone has been investigated in rats and mice (NTP 1989b); this study detected only equivocal evidence of carcinogenicity in male rats, with no evidence of carcinogenicity in female rats or in male or female mice. However, the cancer potential for other organic arsenic compounds has not been studied in chronic bioassays. Since MMA and DMA are formed from inorganic arsenic in vivo by methylation in the liver, chronic studies of the carcinogenic potential of these compounds would be valuable. Studies of humans exposed in the workplace

would probably be preferable to studies in animals, since animals appear to be less susceptible to the carcinogenic effects of arsenic than humans. Studies on cancer risk following chronic dermal exposure to organic arsenicals are probably not essential.

Genotoxicity. There are several studies which suggest that inorganic arsenic may cause genotoxicity (mainly chromosomal effects) in exposed humans (Burgdorf et al. 1977; Nordenson et al. 1978), and this is supported by numerous studies in animals (Datta et al. 1986; DeKnudt et al. 1986; Nagymajtenyi et al. 1985) and cultured cells (Beckman and Nordenson 1986; Casto et al. 1979; DiPaulo and Casto 1979; Lee et al. 1985; Nakamuro and Sayato 1981; Nishioka 1975; Oberly et al. 1982; Okui and Fujiwara 1986; Sweins 1983; Ulitzer and Barak 1988; Zanzoni and Jung 1980). The mechanism of genotoxicity is not known, but may be due to the ability of arsenite to inhibit DNA replicating or repair enzymes (Li and Rossman 1989), or the ability of arsenate to act as a phosphate analog. Further studies to improve our understanding of the mechanism of genotoxicity would be valuable since this could aid in the understanding of arsenic-induced cancer risk.

Reproductive Toxicity. No information was located regarding the effect of inorganic arsenic on gametogenesis or reproductive organ pathology in humans, and only one oral study was located in animals. This study (a three-generation study in mice) detected no significant effects on most end points of reproductive success, although a trend toward decreased pups per litter was noted (Schroeder and Mitchner 1971). Studies on spermatogenesis and reproductive success in arsenic-exposed workers would be valuable in evaluating whether there are significant reproductive risks of arsenic in humans, and this could be further strengthened by similar studies, including histopathological examination of reproductive tissues, in animals.

No information was located on reproductive effects of organic arsenicals in humans, but one study in animals indicated that oral exposure of male mice to MMA could result in a marked decrease in litter production in untreated females (Prukop and Savage 1986). This suggests that spermatogenesis or mating behavior may have been adversely affected, and further studies would be valuable to investigate the mechanism of this effect and whether other organic arsenicals produce similar effects.

Developmental Toxicity. There are several epidemiological studies which suggest that inhalation or oral exposure to inorganic arsenic might increase the risk of low birth weight, congenital defects, or abortion in exposed women (Aschengrau et al. 1989; Nordstrom et al. 1978a, 1978b, 1979a, 1979b; Zierler et al. 1988). These studies do not establish that arsenic was responsible, since all involved exposures to other chemicals or risk factors, but do suggest that additional studies on developmental parameters in humans exposed to arsenic would be valuable in determining whether this is an effect of concern. Studies in animals support the view that oral, inhalation, and parenteral exposure to inorganic arsenic can all increase the incidence of fetotoxicity and teratogenicity, although this appears to occur only at doses that are toxic or even lethal to the dams (Baxley et al. 1981; Beaudoin 1974; Carpenter 1987; Ferm and Carpenter 1968; Ferm et al. 1971; Hanlon and Ferm 1986c; Hood and Bishop 1972; Hood and Harrison 1982; Hood et al. 1978; Mason et al. 1989; Nagymajtenyi et al. 1985; Willhite 1981). Thus, additional studies in animals may be useful in defining the mechanisms of these developmental effects and in identifying the time of maximum susceptibility of the fetus, but such studies probably will not help identify a safe exposure level for humans.

No information was located regarding developmental effects in humans after oral or inhalation exposure to organic arsenicals. One oral study and two intraperitoneal ingestion studies in animals indicate that MMA and DMA can produce developmental effects, but only at levels that cause maternal toxicity (Hood et al. 1982; Rogers et al. 1981; Willhite 1981). However, in view of the apparent differences in susceptibility between animals and humans, it would be valuable to investigate whether there are any measurable effects on development in humans exposed to organic arsenicals in the workplace or the environment.

Immunotoxicity. No studies were located on immunotoxic effects in humans after oral exposure to inorganic arsenic. One inhalation study in humans (Bencko et al. 1988), one oral study in animals (Kerkvliet et al. 1980), and one intratracheal instillation study in animals (Sikorski et al. 1989) suggest that arsenic causes little or no functional impairment of the immune system, but additional studies (both in humans and animals) would be valuable to investigate this end point further. Dermal exposure of humans to high levels of arsenic dusts may cause dermal sensitization (Holmqvist 1951), but the dose and time dependence of this phenomenon are not known. Studies to determine whether dermal sensitization occurs in people with low level dermal exposures to arsenic in dust or soil, such as might occur for residents near an arsenic-containing waste site, would be valuable in assessing the significance of this effect to nonoccupationally exposed populations.

No information was located on the immunotoxicity of organic arsenicals in humans or animals. Since there are suggestions that inorganic arsenic may cause some changes in the immune system, screening level studies on possible immune effects of the common organic arsenicals might be helpful.

Neurotoxicity. There is convincing evidence from studies in humans that inorganic arsenic can cause serious neurological effects, both after inhalation exposure (Beckett et al. 1986; Danan et al. 1984; Morton and Caron 1989) and oral exposure (Armstrong et al. 1984; Feldman et al. 1979; Fincher and Koerker 1987; Huang et al. 1985; Landau et al. 1977; Mizuta et al. 1956; Silver and Wainman 1952). This is based mainly on clinical observations and neurological examinations of exposed persons, and is confirmed by histological examination of nerve biopsy specimens. Available studies provide a reasonable estimate of LOAEL and NOAEL values by the oral route, but similar data are lacking for the inhalation route. Further studies designed to identify the threshold for neurological effects in humans exposed by the inhalation route would be valuable, since humans may be exposed to arsenic dusts in air from smelters, chemical factories, or waste sites. Animals appear to be much less susceptible than humans to the neurological effects of inorganic arsenic, so studies in animals would probably not help in estimation of a safe exposure limit.

No information was located on neurological effects of organic arsenicals in humans, but clear clinical and histological signs of neurotoxicity have been noted in pigs given repeated oral doses of roxarsone (Edmonds and Baker 1986; Kennedy et al. 1986; Rice et al. 1985). These findings suggest that more extensive investigations of the neurotoxic potential of roxarsone and other organic arsenicals would be valuable to determine the potential human health risk from these compounds, since humans could be exposed during the manufacture or use of these compounds, or near waste sites where they have been deposited.

Epidemiological and Human Dosimetry Studies. There have been many epidemiological studies of humans exposed to inorganic arsenic by the oral and inhalation routes, and these studies constitute the core of the database on the cancer and noncancer human health effects of arsenic. As with all epidemiological data sets, these studies are limited by possible confounding from factors such as smoking, exposure to other chemicals, etc. A second major limitation to many of these studies is the difficulty in estimating dose in the exposed members of the cohorts, and some studies lack quantitative data altogether. For this reason, improved data on confounding factors and improved methods of human dosimetry would be very valuable in any further human epidemiological studies, either in the workplace or in the general environment. Availability of methods for biomonitoring of exposure are discussed below.

Biomarkers of Exposure and Effect. There are sensitive and specific methods for measuring arsenic in blood, urine, hair, nails, and other tissues, and this is the approach normally employed for measuring arsenic exposure in humans. Usually total arsenic is measured, but methods are available for measuring inorganic arsenic and each of the organic derivatives separately. Urinary levels are generally considered to be the most reliable indication of recent exposures (Enterline et al. 1987a; Milham and Strong 1974; Pinto et al. 1976; Polissar et al.

1990), but if a high urinary level is present, care must be taken to account for the presence of nontoxic forms of arsenic from the diet. Blood levels are sometimes used to evaluate the status of acutely poisoned individuals (Driesback 1980; Heydorn 1970; Hindmarsh and McCurdy 1986; Valentine et al. 1979, 1981), but this approach is not generally useful for biomonitoring of long-term exposure to low levels. Hair and nails provide a valuable indication of exposures that occurred 1–10 months earlier (Agahian et al. 1990; Bencko et al. 1986; Choucair and Ajax 1988; Landau et al. 1977; Milham and Strong 1974; Southwick et al. 1981; Valentine et al. 1979; Yamauchi et al. 1989), although care must be taken to exclude external contamination of these samples. Cumulative urinary arsenic levels may be used to derive a quantitative estimate of exposure (Enterline et al. 1987a; Pinto et al. 1976), but data on the quantitative relation between exposure and arsenic levels in nails and hair were not located. Efforts to establish an algorithm for estimating past exposure levels from hair or nail levels would be valuable in quantifying average long-term exposure levels in people where repeated urinary monitoring is not feasible.

The effects of arsenic are mainly nonspecific, but the combined presence of several of the most characteristic clinical signs (e.g., nausea, diarrhea, peripheral neuropathy, anemia, vascular lesions, hyperkeratinization, hyperpigmentation) is usually adequate to suggest arsenic intoxication. Although there are standard clinical methods for detecting and evaluating each of these effects, there are no recognized methods for identifying early (preclinical) effects in exposed persons. Neurophysiological measurements of nerve conduction velocity or amplitude have been investigated (Goebel et al. 1990; Jenkins 1966; LeQuesne and McLeod 1977; Morton and Caron 1989; Murphy et al. 1981), but at present this approach does not seem to offer much advantage over a standard neurological examination. Changes in urinary excretion levels of several heme-related metabolites appears to be a good indication of preclinical effects of arsenic toxicity in animals (Albores et al. 1989; Sardana et al. 1981; Woods and Fowler 1978; Woods and Southern 1989), but this has not been established in humans, and is not specific for arsenic-induced effects. Further efforts to develop these approaches and to identify other more specific biochemical or physiological indicators of arsenic-induced effects would be very valuable in monitoring the health of persons exposed to low levels of arsenic in the environment or near waste sites.

Absorption, Distribution, Metabolism, and Excretion. Available data from toxicokinetic studies in humans reveal that arsenates and arsenites are well-absorbed following both oral and inhalation exposure. Data on distribution are limited, but it appears that arsenic is transported to nearly all tissues. Metabolism involves mainly reduction-oxidation reactions that interconvert As(+5) and As(+3), and methylation of As(+3) to yield MMA and DMA. Most arsenic is rapidly excreted in the urine as a mixture of inorganic arsenics, MMA, and DMA, although some may remain bound in tissues (especially skin, hair, and fingernails). These findings are strongly supported by numerous studies in animals. Because methylation represents a detoxification pathway, an area of special interest is the capacity of the human body to methylate inorganic arsenic. Limited data suggest that the methylation system might begin to become saturated at intakes of about 0.2–1 mg As/day (Buchet et al. 1981b; Marcus and Rispin 1988), but this is uncertain. Further studies to define the rate and saturation kinetics of whole body methylation in humans would be especially helpful in evaluating human health risk from the low levels of arsenic intake that are usually encountered in the environment. Along the same line, further studies to determine the nature and magnitude of individual variations in methylation capacity, and how this depends on diet, age, and other factors, would be very useful in understanding and predicting which members of a population are likely to be most susceptible.

The toxicokinetics of dermal exposure have not been studied. It is usually considered that dermal uptake of arsenates and arsenites is sufficiently slow that this route is unlikely to be of health concern (except that due to direct irritation), but studies to test the validity of this assumption would be valuable. Also, dermal uptake of organic arsenicals could be of concern, and quantitative data on the rate and extent of this would be helpful in evaluating risks from application of arsenical pesticides or exposures to organic arsenicals in waste sites.

Comparative Toxicokinetics. Available toxicity data indicate that arsenic causes many of the same effects in animals that are observed in humans, but that animals are significantly less sensitive. The basis for this difference in susceptibility is not certain, but is probably mainly a result of differences in absorption, distribution, metabolism, or excretion. For example, rats strongly retain arsenic in red blood cells (Lanz et al. 1950) while humans (and most other species) do not. Similarly, marmoset monkeys do not methylate inorganic arsenic (Vahter and Marafante 1985; Vahter et al. 1982), while humans and other animal species do. Because of these clear differences in toxicity and toxicokinetics between species, further comparative toxicokinetic studies that focus on the mechanistic basis for these differences would be very valuable. At a minimum, this would help clarify which laboratory species are the most useful models for humans, and could ultimately lead to development of a physiologically based pharmacokinetic model that would permit reliable extrapolation of observations across species.

Methods for Reducing Toxic Effects. There are a number of general methods for reducing the absorption of arsenic in the gastrointestinal tract and skin, but there are currently no methods for reducing the absorption of arsenic from the lungs. The removal of arsenic from the gastrointestinal tract is usually facilitated by the use of emetics, cathartics, lavages, or activated charcoal (Aposhian and Aposhian 1989; ATSDR 1990; Campbell and Alvarez 1989; Driesback 1980; Ellenhorn and Barcelous 1988; EPA 1989e; Haddad and Winchester 1990; Stutz and Janusz 1988). Studies which investigate the effects of phosphate-binding chemicals (aluminum hydroxide) and nonabsorbable sulfhydryl compounds on the absorption of pentavalent and trivalent arsenic, respectively, may be useful in developing treatments which are more specific to arsenic intoxication. Once arsenic is in the body, treatment usually involves the use of one or more chelators such as BAL or penicillamine. However, these agents often exhibit adverse side effects (ATSDR 1990; Ellenhorn and Barceloux 1988). Further studies investigating the efficacy of less toxic arsenic chelators such as DMSA, DMPA, DMPS, and N-acetyl cysteine may lead to the development of safer treatment methods. Studies on the efficacy of chelators in treatment of chronic arsenic exposure would also be helpful. Trivalent arsenic is generally believed to exert toxic effects by binding to the sulfhydryl group of key enzymes, thereby interfering with a number of biological process such as gluconeogenesis and DNA repair (Li and Rossman 1989; Szinicz and Forth 1988). Since pentavalent arsenic may need to be reduced in the body to the trivalent state before it can exert toxic effects, studies which investigate methods for blocking this conversion may lead to a method for interfering with the mechanism of action for pentavalent arsenic.

2.9.3 On-going Studies

A number of researchers are continuing to investigate the toxicity and toxicokinetics of arsenic. Table 2-9 summarizes studies being sponsored by agencies of the U.S. federal government. Additional research is being sponsored by industry groups and other agencies, and research is also ongoing in a number of foreign countries.

TABLE 2-9. On-going Studies on the Health Effects of Arsenic

Investigator	Affiliation	Research description	Sponsor
Anger, K	NIOSH, Cincinnati, Ohio	An epidemiological investigation of the neurologic effects resulting from occupational exposure to various metals, including arsenic	NIOSH, NIH
Barrett, JC	NIEHS, NIH	Examination of the ability of arsenicals to induce morphological transformation, gene mutations and chromosome mutations in Syrian hamster embryo cells	NIEHS, NIH
Bayse, GS	Spelman College	Arsenic detoxification by mammalian tissues	Division of Research Resources, NIH
Carter, DE	University of Arizona	Investigation of the lung and systemic toxicity of particulate gallium arsenide in rats	NIOSH, NIH
Chapin, RE	NIEHS, NIH	Response of rat Sertoli cells (in culture) to arsenic	NIEHS, NIH
Chou, I	Boston University	Mechanism of cell injury induced by metals including As(+3)	NIEHS, NIH
Fowler, BA	University of Maryland	Investigation of gallium arsenide and arsine gas toxicity in animals	NIEHS, NIH
Hong, HL	NIEHS, NIH	Hematopoietic effects resulting from inhalation exposure of mice to arsine gas	NIEHS, NIH
Li, J	NIH (Beijing, China)	Three epidemiologic studies of cancer in China will include dose-response and interactive relations between various factors including arsenic	Division of Cancer Etiology, NIH
Menzel, DB	University of California (Irvine)	Absorption and clearance of metals (including arsenic) associated with flyash and other particulates	NIEHS, NIH
Robins, JM	Harvard University	Improved statistical means for controlling the "healthy worker" effect in epidemiological studies: applied to 8,000 arsenic workers	NIEHS, NIH
Snyder, CA	New York University	Inhalation carcinogenicity of arsenic in the rat	NIEHS, NIH
Thomas, DB	Fred Hutchinson, Cancer Research Center (Seattle, Washington)	An epidemiological study to investigate the relationships between various trace metals (including arsenic) and cancer	NCI, NIH

Sources: CRISP (1990); Federal Research in Progress (1990)

NCI = National Cancer Institute; NIH = National Institutes of Health; NIEHS = National Institute of Environmental Health Sciences; NIOSH = National Institute for Occupational Safety and Health

3. CHEMICAL AND PHYSICAL INFORMATION

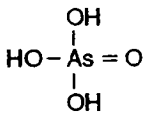
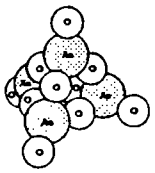
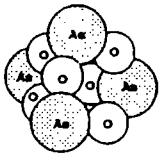
3.1 CHEMICAL IDENTITY

Arsenic can exist in a number of chemical forms. Table 3-1 summarizes information on the formula, structure, names, synonyms, and identification numbers of elemental arsenic and a number of common inorganic compounds. The corresponding information for several common organic arsenicals is presented in Table 3-2.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Table 3-3 summarizes important physical and chemical properties of elemental arsenic and a number of common inorganic compounds. The corresponding information for several common organic arsenicals is presented in Table 3-4.

TABLE 3-1. Chemical Identity of Arsenic and Selected Inorganic Arsenic Compounds[a]

Characteristic	Arsenic	Arsenic acid	Arsenic pentoxide	Arsenic trioxide
Synonym(s)	Arsenic black; colloidal arsenic; gray arsenic	Orthoarsenic acid	Arsenic (V) oxide; arsenic acid anhydride; diarsenic pentoxide	Arsenic oxide; arsenious acid; arsenious oxide; white arsenic
Registered trade name(s)	No data	Dessicant L-10[b]; Scorch[b]	No data	Arsenolite[c,d] Claudelite[c,d]
Chemical formula	As	H_3AsO_4	$As_2O_5(As_4O_{10})$	$As_2O_3(As_4O_6)$
Chemical structure[e]	As			
Identification numbers:				
CAS registry	7440-38-2	7778-39-4	1303-28-2	1327-53-3
NIOSH RTECS	CG0525000	CG0700000	CG2275000	CG3325000
EPA hazardous waste	D004	D004, P011	D004, P011	D004, P012
OHM/TADS	No data	No data	No data	No data
DOT/UN/NA/IMCO shipping	UN1558/ IMCO 6.1	UN1553 (liquid) UN1554 (solid)/ IMCO 6.1	UN1559/ IMCO 6.1	UN1561/ IMCO 6.1
HSDB	509	431	429	419
NCI	No data	No data	No data	No data

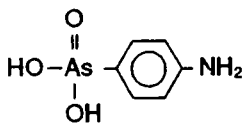
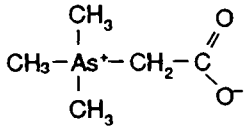
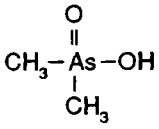
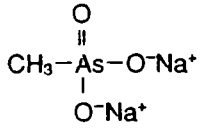
[a]All information obtained from HSDB 1990 except where noted.
[b]Sitting 1980
[c]Sax and Lewis 1989
[d]IARC 1980
[e]Cotton and Wilkinson 1962

CAS = Chemical Abstracts Services; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

TABLE 3-1 (Continued)

Characteristic	Calcium arsenate	Gallium arsenide	Sodium arsenate	Sodium arsenite
Synonym(s)	Calcium orthoarsenate; arsenic acid, calcium salt	Gallium monoarsenide	Disodium arsenate; sodium biarsenate; arsenic acid, disodium salt	Arsenious acid, sodium salt; sodium metaarsenite
Registered trade name(s)	Pencal®[b] Spra-cal®[d]	No data	No data	Atlas A®[b]; Chem Sen®[b]; Kill-All®[b]
Chemical formula	$Ca_3(AsO_4)_2$	GaAs	Na_2HAsO_4	$NaAsO_2$[c]
Chemical structure[e]	$(Ca^{+2})_3\ (O-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{As}}-O^{-3})_2$	Ga:As	$Na^+\ ^-O-\overset{\overset{O}{\|}}{\underset{\underset{O^-\,Na^+}{\|}}{As}}-OH$	$O=As-O^-\,Na^+$
Identification numbers:				
CAS registry	7778-44-1	1303-00-0	7778-43-0	7784-46-5
NIOSH RTECS	CG0830000	LW8800000	CG0875000	CG3675000
EPA hazardous waste	D004	No data	No data	No data
OHM/TADS	No data	No data	No data	7800057
DOT/UN/NA/IMCO shipping	UN1573 IMCO 6.1	No data	No data	UN1686 (liquid) UN2027 (solid) IMCO 6.1
HSDB	1433	4376	1675	693
NCI	No data	No data	No data	No data

TABLE 3-2. Chemical Identity of Selected Organic Arsenic Compounds[a]

Characteristic	Arsanilic acid	Arsenobetaine	Dimethylarsinic acid	Disodium methanearsonate
Synonym(s)	4-Aminophenyl-arsonic acid; atoxilic acid	Fish arsenic	Cacodylic acid; DMA; DMAA; hydroxy-dimethylarsinic acid	DSMA[b], methyl-arsonic acid, disodium salt; disodium methyl arsonate
Registered trade name(s)	Premix®[d] Pro Gen®[d]	No data	Ansar®[b] Arsan®[b] Silvisar®[b] Phytar®[b]	Crab-E-Rad®[b]; Methar®[b] Sodar®[b]
Chemical formula	$(C_6H_4NH_2)H_2AsO_3$	$(CH_3)_3As^+CH_2CO_2^-$	$(CH_3)_2HAsO_2$	$CH_3Na_2AsO_3$
Chemical structure[e]				
Identification numbers:				
CAS registry	98-50-0	64436-13-1	75-60-5	144-21-8
NIOSH RTECS	CF7875000	No data	CH7525000	PA2275000
EPA hazardous waste	No data	No data	No data	K084; K101; K102
OHM/TADS	No data	No data	No data	No data
DOT/UN/NA/IMCO shipping	No data	No data	No data	No data UN1556 (liquid) UN1557 (solid)
HSDB				
NCI	432 No data	No data No data	160 No data	1701 No data

[a]All information obtained from HSDB 1990 except where noted.
[b]Sittig 1980
[c]EPA 1982c
[d]IARC 1980
[e]NAS 1977a

CAS = Chemical Abstracts Services; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

TABLE 3-2 (Continued)

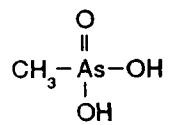
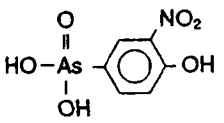
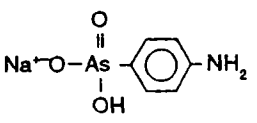
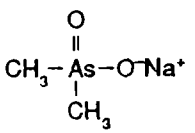
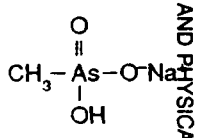
Characteristic	Methanearsonic acid	3-Nitro-4-hydroxy-phenylarsonic acid	Sodium arsanilate	Sodium dimethylarsinate	Sodium methanearsonate
Synonym(s)	Arsonic acid, methyl-; monomethylarsonic acid; MMA	4-Hydroxy-3-nitrophenylarsonic acid; 3-Nitro-10; roxarsone	Arsamin; arsanilic acid, sodium salt; sodium p-arsanilate	Sodium cacodylate, cacodylic acid, sodium salt	MSMA;[b] monosodium methanearsenic[b]
Registered trade name(s)	No data	No data	No data	Sivisar® Ansar Phytar®	Bueno®[b] Daconate®[b] Phyban®[b]
Chemical formula	$CH_3H_2AsO_3$	$(C_6H_3OHNO_2)H_2AsO_3$	$(C_6H_4NH_2)NaHAsO_3$	$(CH_3)_2NaAsO_2$	$CH_3NaHAsO_3$
Chemical structure[e]					
Identification numbers:					
CAS registry	124-58-3	121-19-7	127-85-5	124-65-2	2163-80-6[c]
NIOSH RTECS	PA1575000	CY5250000	CF9625000	CH7700000	8A2625000
EPA hazardous waste	K031	No data	No data	No data	No data
OHM/TADS	No data	No data	No data	No data	No data
DOT/UN/NA/IMCO shipping	No data	No data	No data	IMCO 6.1/ UN1688	No data
HSDB	845	4296	5189	731	754
NCI	No data	No data	No data	No data	No data

TABLE 3-3. Physical and Chemical Properties of Arsenic and Selected Inorganic Arsenic Compounds[a]

Property	Arsenic	Arsenic acid	Arsenic pentoxide	Arsenic trioxide
Valence	0[b]	+5[b]	+5[b]	+3[b]
Molecular weight	74.92	150.95[f]	229.84	197.84
Color	Gray	White	White	White[d]
Physical state	Solid	Solid	Solid	Solid[d]
Melting point	817°C at 28 atm	35.5°C	Decomposes at 315°C	312.3°C
Boiling point	613°C sublimes	Loses H_2O at 160°C	No data	465°C[d]
Density	5.727 g/cm^3	2.0-2.5 g/cm^3	4.32 g/cm^3	3.738 g/cm^3
Odor	Odorless[e]	No data	No data	Odorless[e]
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility:				
Water	Insoluble	3,020 g/L at 12.5°C	1,500 g/L at 16°C[e] 658 g/L at 20°C[c] 767 g/L at 100°C	37 g/L at 20°C 101 g/L at 100°C
Organic solvent(s)	No data	Soluble in alcohol	Soluble in alcohol	Soluble in glycerin, slightly soluble in alcohol[e]
Acids	Soluble in nitric acid	No data	Soluble in acid[e]	Soluble in HCl[b]
Partition coefficients:				
Log K_{ow}	No data	No data	No data	No data
Log K_{oc}	No data	No data	No data	No data
Vapor pressure	1 mmHg at 372°C[e] 40 mmHg at 483°C[e] 100 mmHg at 518°C[e]	No data	No data	66.1 mmHg at 312°C[e]
Henry's law constant	No data	No data	No data	No data
Autoignition temperature	No data	No data	No data	Nonflammable[e]
Flashpoint	No data	No data	No data	No data
Flammability limits	No data	No data	No data	No data
Conversion factors	No data	No data	No data	No data
Explosive limits	No data	No data	No data	No data

[a]All information obtained from Weast 1985 unless otherwise noted.
[b]EPA 1982c
[c]Sax and Lewis 1989
[d]Budavari et al. 1989
[e]HSDB 1990
[f]Value for $H_3AsO_4 \cdot 1/2\ H_2O$

TABLE 3-3 (Continued)

Property	Calcium arsenate	Gallium arsenide	Sodium arsenate	Sodium arsenite
Valence	+5[b]	-3	+5	+3
Molecular weight	398.08	144.64	185.91[e]	129.91
Color	Colorless[c]	Dark gray	No data	Gray-white
Physical state	Solid	Solid	Solid[d]	Solid
Melting point	1.455°C	1238°C	57°C[d]	No data
Boiling point	No data	No data	No data	No data
Density	3.62 g/cm^3	5.31[d] g/cm^3	1.87[d] g/cm^3	1.87 g/cm^3
Odor	Odorless[e]	No data	Odorless[d]	No data
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility:				
Water	0.13 g/L at 25°C	No data	Soluble[d]	Very soluble
Organic solvent(s)	Insoluble	No data	Slightly soluble in alcohol[d]	Slightly soluble in alcohol
Acids	Soluble in dilute acids[e]	No data	No data	No data
Partition coefficients:				
Log K_{ow}	No data	No data	No data	No data
Log K_{oc}	No data	No data	No data	No data
Vapor pressure	No data	No data	No data	No data
Henry's law constant	No data	No data	No data	No data
Autoignition temperature	No data	No data	No data	No data
Flashpoint	No data	No data	No data	No data
Flammability limits	No data	No data	No data	No data
Conversion factors	No data	No data	No data	No data
Explosive limits	No data	No data	No data	No data

TABLE 3-4. Physical and Chemical Properties of Selected Organic Arsenic Compounds[a]

Property	Arsanilic acid	Arsenobetaine	Dimethylarsinic acid	Disodium methanearsonate
Molecular weight	217.06[c]	178.06[b]	138.01[b]	183.9[g]
Color	White[b]	No data	Colorless[b]	Colorless[b]
Physical state	Solid	Solid[b]	Solid[d]	Solid[b]
Melting point	232°C[c]	204-210°C[b]	195-196°C[d]	>355°C[b]
Boiling point	Loses H_2O at 15°C[c]	No data	No data	No data
Density	1.9571[b] g/cm^3	No data	No data	No data
Odor	Practically odorless[b]	No data	Odorless[b]	No data
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility:				
Water	Very soluble in hot water[c]	No data	660 g/L at 25°C[f]	1,000 g/L[b]
Organic solvent(s)	Soluble in alcohol, insoluble in ether[c]	Soluble in alcohol[b]	Very soluble in alcohol[d]	Slightly soluble in alcohol[b]
Acids	Slightly soluble in acetic acid[b]	No data	Soluble in acetic acid[d]	No data
Partition coefficients:				
Log K_{ow}	No data	No data	No data	No data
Log K_{oc}	No data	No data	No data	No data
Vapor pressure	No data	No data	No data	No data
Henry's law constant	No data	No data	No data	No data
Autoignition temperature	No data	No data	No data	No data
Flashpoint	No data	No data	No data	No data
Flammability limits	No data	No data	No data	No data
Conversion factors	No data	No data	No data	No data
Explosive limits	No data	No data	No data	No data

[a]All information obtained from Weast 1985 unless otherwise noted.
[b]HSDB 1990
[c]Sax and Lewis 1989
[d]Budavari et al. 1989
[e]EPA 1982c
[f]Hood 1985
[g]IARC 1980

TABLE 3-4 (Continued)

Property	Methane arsonic acid	3-Nitro-4-hydroxy-phenylarsonic acid	Sodium arsanilate	Sodium dimethylarsinate	Sodium methanearsonate
Molecular weight	139.98[b]	263.03[b]	239.05[c]	159.98[b]	161.96[b]
Color	White	Pale yellow	White[c]	Colorless[b]	No data
Physical state	Solid	Solid[b]	Solid[c]	Solid[d]	No data
Melting point	161°C[d]	No data	No data	200°C[b]	115-119°C[e]
Boiling point	No data	No data	No data	No data	No data
Density	No data	No data	No data	No data	No data
Odor	No data	No data	Odorless[c]	Slight odor[d]	No data
Odor threshold:					
Water	No data	No data	No data	No data	No data
Air	No data	No data	No data	No data	No data
Solubility:					
Water	Soluble[d]	Slightly soluble[b]	Soluble[c]	830 g/L at 22°C[d]	570 g/L at 25°C[e]
Organic solvent(s)	Soluble in alcohol[d]	Soluble in alcohol, acetone[b]	Slightly soluble in alcohol[c]	No data	No data
Acids	No data	Soluble in acetic acid[b]	No data	No data	No data
Partition coefficients:					
Log K_{ow}	No data	No data	No data	No data	No data
Log K_{oc}	No data	No data	No data	No data	No data
Vapor pressure	No data	No data	No data	No data	No data
Henry's law constant	No data	No data	No data	No data	No data
Autoignition temperature	No data	No data	No data	No data	No data
Flashpoint	No data	No data	No data	No data	No data
Flammability limits	No data	No data	No data	No data	No data
Conversion factors	No data	No data	No data	No data	No data
Explosive limits	No data	No data	No data	No data	No data

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

4.1 PRODUCTION

Arsenic is the 20th most abundant element in the earth's crust. It occurs most often as the sulfide in a variety of complex minerals containing copper, lead, iron, nickel, cobalt, and other metals (Budavari et al. 1989; Eisler 1988).

Arsenic trioxide (As_2O_3) is the arsenic compound of chief commercial importance. It is produced primarily from flue dust that is generated at copper and lead smelters. These dusts are collected and purified by roasting with pyrite or galena to yield an arsenic trioxide that is 90–95% pure. Production of elemental arsenic is achieved by the reduction of the trioxide with carbon (EPA 1982c; HSDB 1990).

In the past, arsenic trioxide was produced in the United States at the ASARCO smelter in Tacoma, Washington. Annual production was about 16 million pounds in 1983, but decreased to about 5 million pounds in 1985. After 1985, the ASARCO smelter ceased operation, and arsenic trioxide is no longer produced in the United States (U.S. Bureau of Mines 1988, 1990).

Although arsenic trioxide is not produced in the United States, several U.S. companies use significant quantities of imported material (see Section 4.2), mainly for the formulation of arsenic-containing agricultural chemicals (e.g., pesticides) or wood preservatives. Other companies generate arsenic-containing compounds as by-products of production processes or as impurities. Table 4-1 summarizes the information on U.S. companies that reported the use or generation of arsenic in 1988 to the Toxics Release Inventory (TRI) database (TRI88 1990). The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list.

4.2 IMPORT/EXPORT

Imports of arsenic trioxide to the United States have increased steadily and substantially in recent years, rising from about 35 million pounds in 1985 to an estimated 66 million pounds in 1989 (HSDB 1990; U.S. Bureau of Mines 1990). Imports of elemental arsenic ranged from 0.9 to 1 million pounds during the period from 1985 to 1988, but increased to 2.6 million pounds in 1989 (U.S. Bureau of Mines 1990).

The United States exports only small amounts of arsenic compounds (arsenic acid, sodium arsenate, lead arsenate, and other miscellaneous compounds), ranging from about 0.4 million pounds in 1985 to 0.9 million pounds in 1988 (U.S. Bureau of Mines 1990).

4.3 USE

Currently, the principal use of arsenic (as arsenic trioxide) is in products used for wood preservation (74%). Most of the rest (about 19% of the total) is used in the production of agricultural chemicals such as insecticides, herbicides, algicides, and growth stimulants for plants and animals. Some arsenic formulations which were used in the past as pesticides (e.g., rat or ant poisons) have been prohibited because of concerns about human health risk during production and application, or accidental poisoning at the point of use (see Chapter 7). Smaller amounts of arsenic are also used in the production of glass and nonferrous alloys, and in the electronics industry (Eisler 1988; NTP 1989b; U.S. Bureau of Mines 1990).

TABLE 4-1. Facilities That Manufacture or Process Arsenic[a]

State[b]	Number of facilities	Range of maximum amounts on site in thousands of pounds[c]	Activities and uses[d]
AL	28 (5)*	1-999	8, 9, 13
AR	13	1-999	8, 9, 13
AZ	3 (1)*	10-999	1, 2, 3, 4, 5, 6, 7, 9
CA	8	0-999	1, 4, 5, 7, 8, 9, 13
CO	3 (1)*	0-99	2, 8, 9, 13
FL	15 (1)*	1-999	3, 9
GA	30 (2)*	1-49,999	1, 2, 3, 4, 6, 7, 8, 9
HI	2	10-99	8, 9
IA	2	10-999	1, 3, 4, 7, 8
IL	10	1-999	1, 2, 3, 4, 6, 8, 9, 11, 13
IN	7	0-99	3, 8, 9
KY	8 (1)*	0-999	2, 3, 7, 8, 9
LA	10	10-499,999	2, 3, 6, 7, 8, 9, 10, 12
MA	3	1-99	8, 9
MD	9 (2)*	1-99	8, 9
ME	1	10-99	8
MI	10 (2)*	1-99	3, 8, 9
MN	4	0.1-99	1, 6, 8, 9
MO	7 (1)*	10-99	1, 2, 3, 4, 5, 7, 8, 9, 10
MS	8	1-999	2, 3, 4, 7, 8, 9, 10
MT	3 (2)*	10,000-49,999	1, 2, 3, 4, 5, 6, 7, 8
NC	25 (2)*	1-9,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11
NE	1	100-999	1, 2, 5, 7
NH	1	1-9	9
NJ	9 (1)*	0-999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10
NM	1	10-99	8
NY	7	1-999	2, 3, 8, 9
OH	12	0-99	1, 2, 3, 6, 8, 9
OK	3	0.1-99	2, 3, 6, 8, 9
OR	5 (1)*	10-99	8, 9
PA	14 (2)*	0.1-999	1, 2, 3, 7, 8, 9
PR	3	10-99	9
RI	2	1-99	8
SC	10	10-999	7, 8, 9
TN	10	1-9,999	1, 2, 3, 4, 5, 7, 8, 9
TX	16	1-49,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 12
UT	1	10,000-49,999	1, 5
VA	19 (1)*	0-499,999	2, 3, 6, 8, 9, 11
WA	5	10-999	8, 9
WI	6	0.1-99	8, 9
WV	3	0.1-99	2, 3, 8

[a]TRI88 (1990)
[b]Post office state abbreviations used
[c]Data in TRI are maximum amounts on site at each facility.
[d]Activities/Uses:

1. produce
2. import
3. for on-site use/processing
4. for sale/distribution
5. as a byproduct
6. as an impurity
7. as a reactant
8. as a formulation component
9. as an article component
10. for repackaging only
11. as a chemical processing aid
12. as a manufacturing aid
13. ancillary or other use

*Number of facilities reporting "no data" regarding maximum amount of the substance on site.

Arsenic compounds have a long history of use in medicine where they have been used in the treatment of syphilis, yaws, amoebic dysentery, and trypanosomiasis. The use of organic arsenic compounds to treat venereal disease ceased upon the discovery of antibiotics, but several arsenic compounds are still being used to treat certain severe parasitic diseases (Eisler 1988).

4.4 DISPOSAL

Wastes containing arsenic are considered hazardous wastes and as such their treatment, storage, and disposal are regulated by law (see Chapter 7). The main route of disposal of solid wastes containing arsenic is landfilling. According to the Toxics Release Inventory (TRI88 1990), over 5 million pounds of waste arsenic were disposed of in this way in 1988, nearly all to approved and permitted waste treatment or storage facilities (EPA 1990e). Other disposal alternatives for arsenic-containing wastes include incineration and recycling. There is, however, essentially no recycling of arsenic from its principal uses in wood preservatives or agricultural chemicals (IRPTC 1990; U.S. Bureau of Mines 1990).

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Arsenic is an element that occurs naturally in a variety of sulfidic ores. Arsenic can be released to the environment from natural sources (e.g., volcanoes, erosion from mineral deposits), but releases from human activities (e.g., metal smelting, chemical production and use, coal combustion, waste disposal) can lead to substantial environmental contamination. Most human releases of arsenic are to land or soil, primarily in the form of pesticides or solid wastes. However, substantial amounts are also released to air and to water.

Arsenic released to land is relatively nonmobile, due to binding to soil particles. However, rainwater or snowmelt may leach soluble forms into surface water or groundwater, and soil microorganisms may reduce a small amount to volatile forms (arsines). Arsenic dissolved in water can undergo either reduction or oxidation, depending on conditions. Poorly soluble forms tend to adsorb to organic material in sediments or soils, while the soluble species tend to move with water. Arsenic released to air exists mainly in the form of particulate matter. These particles are dispersed by the wind as a function of their size, and the particles are then returned to the earth by wet or dry deposition. Arsines that are released from microbial sources in soils or sediments undergo oxidation in the air, reconverting the arsenic to nonvolatile forms that settle back to the ground.

Because arsenic is a natural component of the earth's crust, low levels are found in all environmental media. Concentrations in air in remote locations (away from human releases) range from 1 to 3 ng/m^3, while concentrations in cities may range from 20 to 100 ng/m^3. Concentrations in water are usually less than 10 ppb, although higher values can occur near natural mineral deposits or man-made sources. Natural levels of arsenic in soil usually range from 1 to 40 ppm, but pesticide application or waste disposal can produce much higher values. Arsenic is also found in many foods, at concentrations that usually range from 20 to 140 ppb. Concentrations may be substantially higher in certain seafoods, although much of this is in a nontoxic form.

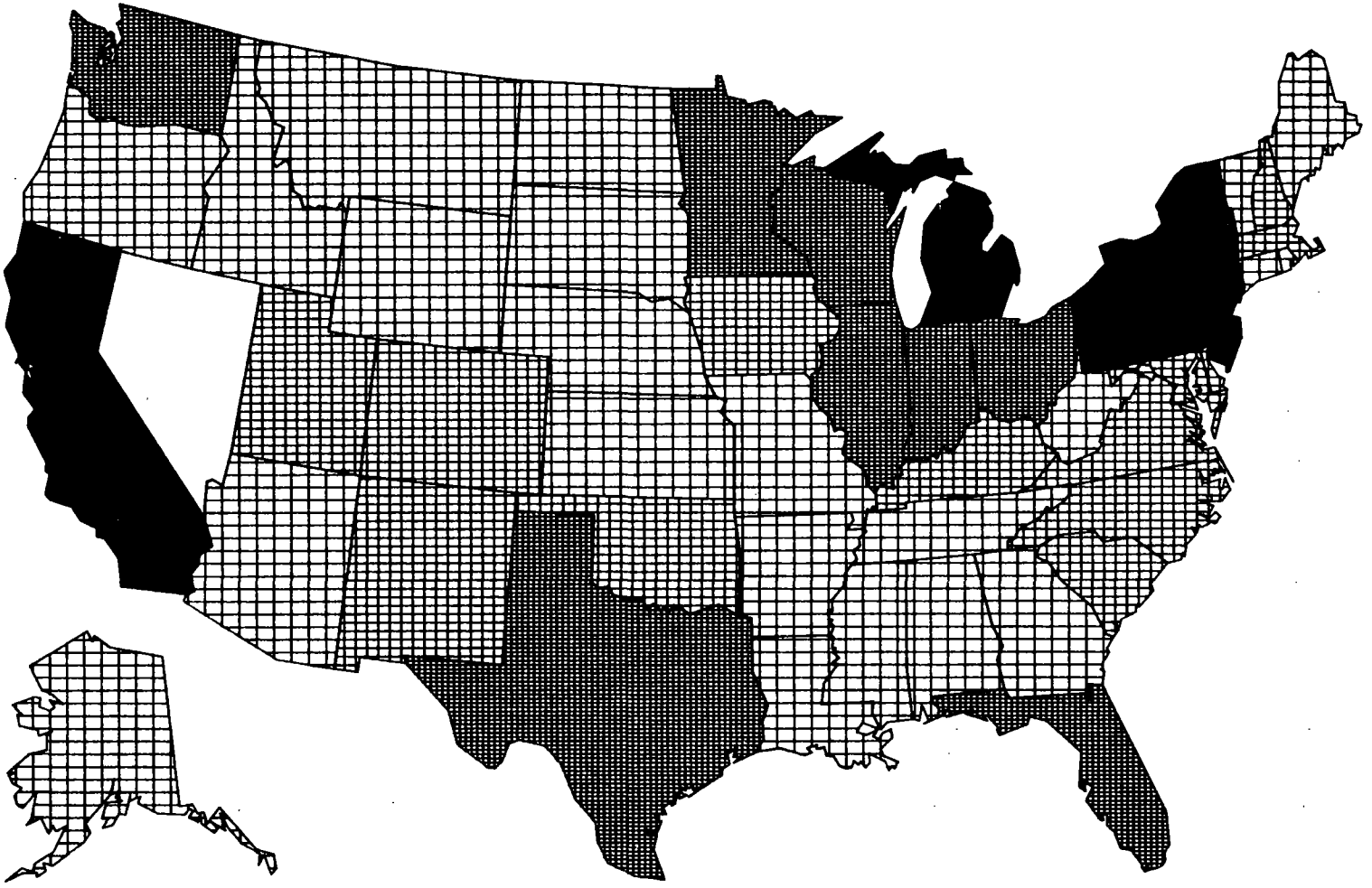
For most people, the diet is the largest source of exposure, with average intakes of about 50 μg/day. Intake from air, soil, and water are usually much smaller, but exposure from these media may become significant in areas of arsenic contamination. People who produce or use arsenic compounds in occupations such as nonferrous metal smelting, pesticide manufacturing or application, wood preservation, semiconductor manufacturing, or glass production can be exposed to substantially higher levels of arsenic, mainly from dusts or aerosols in air. The government estimates that in the early 1980s, about 55,000 workers were exposed in these occupations.

Hazardous waste sites are another possible source of human exposure to arsenic. Arsenic has been identified at 781 of the 1,300 hazardous waste sites that have been proposed for inclusion on the NPL (HAZDAT 1992). The frequency of these sites within the United States can be seen in Figure 5-1. Of these sites 774 are located in the United States and 7 are located in the Commonwealth of Puerto Rico. Exposure at waste sites may occur by a variety of pathways, including inhalation of dusts in air, ingestion of contaminated soil or water, or through the food chain. The magnitude of the exposures may be substantial, but this can only be evaluated on a site-by-site basis.

5.2 RELEASES TO THE ENVIRONMENT

Table 5-1 summarizes data on industrial emissions of arsenic reported to the EPA (TRI88 1990). These data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Further information on arsenic releases to the environment from industrial and other sources is presented below.

FIGURE 5-1. FREQUENCY OF NPL SITES WITH ARSENIC CONTAMINATION *



*Derived from HAZDAT 1992

TABLE 5-1. Releases to the Environment from Facilities That Manufacture or Process Arsenic[a]

State[c]	Number of facilities	Range of reported amounts released in thousands of pounds[b]						
		Air	Underground injection	Water	Land	Total Environment[d]	POTW transfer	Off-site waste transfer
AL	28	0-0.3	0-0	0-0.1	0-0.1	0-0.4	0-0.1	0-1.9
AR	13	0-0.5	0-0	0-0.1	0-0.1	0-0.5	0-0	0-0.5
AZ	3	0-40	0-0	0-0.3	0-2,050	0-2,090	0-0.3	0-0
CA	8	0-6.2	0-0	0-0	0-76.7	0-82.9	0-1.9	0.1-26
CO	3	0-0.1	0-0	0-0	0-0	0-0.1	0-0.1	0.1-0.3
FL	15	0-0.3	0-0	0-0	0-0	0-0.3	0-0	0-2.4
GA	30	0-0.5	0-0	0-0.3	0-0	0-0.5	0-0.3	0-126.5
HI	2	0-0	0-0	0-0	0-0	0-0	0-0	0-0.8
IA	2	0-0	0-0	0-0.3	0-0	0-0.3	0-0.1	0.3-82
IL	10	0-2	0-21.7	0-0.1	0-0	0-21.7	0-0.3	0-1.2
IN	7	0-0.3	0-0	0-0	0-0	0-0.3	0-0.1	0-91
KY	8	0-0.5	0-0	0-0	0-0	0-0.5	0-0	0-0.8
LA	10	0-2.8	0-0	0-0.3	0-1	0-2.8	0-0	0-2.9
MA	3	0-0	0-0	0-0	0-0	0-0	0-0	0.3-0.3
MD	9	0-0.3	0-0	0-0	0-0	0-0.3	0-0	0-19.3
ME	1	0-0	0-0	0-0	0-0	0-0	0-0	0.3-0.3
MI	10	0-0.3	0-0	0-0	0-0	0-0.3	0-0	0-0.3
MN	4	0.1-0.3	0-0	0-0.2	0-7.6	0.1-7.8	0-0.1	0-1.1
MO	7	0-0.3	0-0	0-0.3	0-6.5	0-6.5	0-0	0-0.3
MS	8	0-0.5	0-0	0-0.3	0-0.3	0-1	0-0	0-0.5
MT	3	0-52	0-0	0-0	0-209.5	0-261.5	0-0.1	0-0.3
NC	25	0-0.5	0-0	0-0.3	0-0.3	0-1	0-0.3	0-550
NE	1	2-2	0-0	0.3-0.3	0.8-0.8	3-3	0.3-0.3	134-134
NH	1	0.3-0.3	0-0	0-0	0-0	0.3-0.3	0-0	0.3-0.3
NJ	9	0-0.3	0-0	0-0	0-0.1	0-0.3	0-0.3	0-0.5
NM	1	0-0	0-0	0-0	0-0	0-0	0-0	0.3-0.3
NY	7	0-2.9	0-0	0-0	0-0	0-2.9	0-0.2	0.2-15.8
OH	12	0-0.5	0-0	0-0	0-0.3	0-0.5	0-0	0-0.9
OK	3	0-0.1	0-0	0-0.3	0-0.3	0.1-0.5	0-0	0-0.8
OR	5	0-0.1	0-0	0-0.1	0-0	0-0.1	0-0	0-0.4
PA	14	0-0.8	0-0	0-0.3	0-0	0-0.8	0-0	0-36.6
PR	3	0-0.3	0-0	0-0	0-0	0-0.3	0-0	0-0.3
RI	2	0-1.1	0-0	0-0	0-0	0-1.1	0-0	0.3-1.4
SC	10	0-5.3	0-0	0-0.1	0-0	0-5.3	0-0	0-15.3
TN	10	0-0.6	0-0	0-0	0-4.8	0-4.9	0-0.1	0-22.7
TX	16	0-46.3	0-5.7	0-0.3	0-430.8	0-477.1	0-0.8	0-117.6
UT	1	12.8-12.8	0-0	2.8-2.8	2,600-2,600	2,615-2,615	0-0	0-0
VA	19	0-0.5	0-0	0-0.1	0-0.3	0-0.5	0-0	0-3.5
WA	5	0-0.3	0-0	0-0.8	0-0.1	0.1-0.8	0-0.1	0.1-0.8
WI	6	0-0.3	0-0	0-0	0-0	0-0.3	0-0	0-1.2
WV	3	0-61.4	0-0	0-0.3	0-0	0-61.6	0-0	0-30.6

[a]TRI88 (1990)
[b]Data in TRI are maximum amounts released by each facility. Quantities reported here have been rounded to the nearest hundred pounds, except those quantities (1 million pounds which have been rounded to the nearest thousand pounds.
[c]Post office state abbreviation used
[d]The sum of all releases of the chemical to air, land, water, and underground injection wells by a given facility.

POTW = Publicly owned treatment works

5.2.1 Air

Estimated total releases of arsenic to air in the late 1970s from production of arsenic, use of arsenic-containing products, and other miscellaneous sources ranged from about 13 to 19 million pounds (EPA 1982a, 1982c). It is likely that air releases of arsenic have decreased in the past decade due to recent regulations on industrial emissions (EPA 1986f), improved control technology for coal-burning facilities, and the decreased use of arsenical pesticides. For example, emissions from industrial sources to air reported to the TRI database for 1988 totaled only about 270,000 pounds (TRI88 1990). As noted above, however, these data should be used with caution since only certain types of facilities are required to report. Also, these data do not include emissions from coal combustion facilities or pesticide spraying, two major additional arsenic sources.

An average of about 17 million pounds per year of arsenic may also be released to the air from natural phenomena, including volcanic eruptions and forest fires (Walsh et al. 1979). On a global scale, this is probably greater than the amount currently released to air by human activity (see above). However, industrial activities are the main local sources of arsenic releases to the atmosphere (EPA 1982a, 1982c, 1984a; NAS 1977a).

5.2.2 Water

Arsenic may be released to water by natural weathering processes, by discharge from industrial facilities, by leaching from landfills or soil, or by urban runoff (EPA 1982a; Francis and White 1987; IARC 1980; Wadge and Hutton 1987). Reported industrial discharges of arsenic compounds to surface water and public sewage treatment works for 1988 totalled 7,500 and 5,100 pounds, respectively (TRI88 1990). Underground injection (which can lead to groundwater contamination) totalled 27,400 pounds. Arsenic was detected in 58% of samples of urban stormwater runoff from 8 of 15 cities surveyed in the National Urban Runoff Program at concentrations ranging from 1 to 50.5 ppb (Cole et al. 1984).

Arsenic has been detected in both surface water and groundwater at about 15% of hazardous waste sites for which data are included in the Contract Laboratory Program (CLP) Statistical Database (CLPSD 1990). Note that the CLP Statistical Database includes data from both NPL and non-NPL sites. The geometric mean arsenic concentrations of the positive samples were about 40 and 47 ppb for groundwater and surface water, respectively, at these sites (CLPSD 1990).

5.2.3 Soil

Most arsenic (about 80% of the total) that is released to the environment from human activities is released to soil (EPA 1982c). Application of pesticides and disposal of solid wastes from fossil fuel combustion and industrial processes are the major sources. Reported releases to land from industrial processes totalled about 5.6 million pounds in 1988 (TRI88 1990), accounting for nearly 95% of total reported environment releases. Of this, nearly all was to permitted facilities (EPA 1990e). Land application of sewage sludge is another source of arsenic in soil. Arsenic was detected in sewage sludge samples from 23 cities at concentrations of 0.3–53 ppm (Mumma et al. 1984).

Arsenic has been detected in soil at 16% of 385 hazardous waste sites where it has been measured, at a geometric mean concentration of 5 ppm (CLPSD 1990). The maximum reported soil concentration from the CLPSD was 5,000 ppm (Eckel and Langley 1988). Based on comparison with average background levels of arsenic in soil (see Section 5.4.3), these data indicate that arsenic detected in soil at some waste sites may be natural and not the result of waste disposal.

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

Most arsenic in the environment exists in soil or rock. This material may be transported by wind or water erosion of small particles, or may be transported by leaching into rainfall or snowmelt. However, because many arsenic compounds tend to adsorb to soils or sediments, leaching usually results in transportation over only short distances in soil (EPA 1982c; Moore et al. 1988; Welch et al. 1988).

Transport and partitioning of arsenic in water depends upon the chemical form (oxidation state and counter ion) of the arsenic and on interactions with other materials present. Soluble forms move with the water, and may be carried long distances through rivers (Callahan et al. 1979). However, arsenic may be adsorbed from water onto sediments or soils, especially clays, iron oxides, aluminum hydroxides, manganese compounds, and organic material (Callahan et al. 1979; EPA 1982c; Welch et al. 1988). Sediment-bound arsenic may be released back into the water by chemical or biological interconversions of arsenic species (see Section 5.3.2).

Arsenic in the atmosphere exists as particulate matter, mostly as particles less than 2 μm in diameter (Coles et al. 1979). These particles are transported by wind and air currents until they are returned to earth by wet or dry deposition. The residence time of particulate-bound arsenic depends on particle size and meteorological conditions, but a typical value is about 9 days (EPA 1982a).

Bioconcentration of arsenic occurs in aquatic organisms, primarily in algae and lower invertebrates. Bioconcentration factors (BCFs) measured in freshwater invertebrates and fish for several arsenic compounds ranged from 0 to 17, but a BCF of 350 was observed in marine oysters (EPA 1980a). Biomagnification in aquatic food chains does not appear to be significant (Callahan et al. 1979; EPA 1982a, 1983e), although some fish and invertebrates contain high levels of arsenic compounds. Terrestrial plants may accumulate arsenic by root uptake from the soil or by absorption of airborne arsenic deposited on the leaves, and certain species may accumulate substantial levels (EPA 1982a).

5.3.2 Transformation and Degradation

5.3.2.1 Air

Arsenic is released into the atmosphere primarily as arsenic trioxide or, less frequently, in one of several volatile organic compounds, mainly arsines (EPA 1982a). Trivalent arsenic and methyl arsines in the atmosphere undergo oxidation to the pentavalent state (EPA 1984a), and arsenic in the atmosphere is usually a mixture of the trivalent and pentavalent forms (EPA 1984a; Scudlark and Church 1988). Photolysis is not considered an important fate process for arsenic compounds (Callahan et al. 1979).

5.3.2.2 Water

Arsenic in water can undergo a complex series of transformations, including oxidation-reduction reactions, ligand exchange, and biotransformation (Callahan et al. 1979; EPA 1984a; Welch et al. 1988). Rate constants for these various reactions are not readily available, but the factors most strongly influencing fate processes in water include Eh (the oxidation-reduction potential), pH, metal sulfide and sulfide ion concentrations, iron concentrations, temperature, salinity, and distribution and composition of the biota (Callahan et al. 1979; Wakao et al. 1988). The predominant form of arsenic in surface waters is usually arsenate (EPA 1982c), but aquatic microorganisms may reduce the arsenate to arsenite and a variety of methylated arsenicals (Benson 1989;

Braman and Foreback 1973; Edmonds and Francesconi 1987). Arsenate also often predominates in groundwater, but arsenite may be an important component, depending upon the characteristics of the water and surrounding geology (Robertson 1989; Welch et al. 1988).

5.3.2.3 Soil

Transformations of arsenic in soil are similar to those occurring in aquatic systems, with As(+5) predominating in aerobic soils, As(+3) in slightly reduced soils (e.g., temporarily flooded), and arsine, methylated arsenic, and elemental arsenic in very reduced conditions (e.g., swamps and bogs) (EPA 1982a). Organoarsenical pesticides (e.g., MMA, DMA) applied to soil are metabolized by soil bacteria to alkylarsines, arsenate, and MMA (Hood 1985). The half-life of DMA in soil is about 20 days (Hood 1985).

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 Air

Arsenic in ambient air is usually a mixture of arsenite and arsenate, with organic species of negligible importance except in areas of substantial methylated arsenic pesticide application or biotic activity (EPA 1984a). Mean levels in ambient air in the United States usually range from <1 to 3 ng/m^3 in remote areas and from 20 to 30 ng/m^3 in urban areas (Davidson et al. 1985; EPA 1982c; IARC 1980; NAS 1977a). Large cities generally have higher arsenic air concentrations than smaller ones due to emissions from coal-fired power plants (IARC 1980), but maximum 24-hour concentrations generally are less than 100 ng/m^3 (EPA 1984a). The highest arsenic levels detected in the atmosphere were near nonferrous metal smelters, with reported concentrations up to 2,500 ng/m^3 (IARC 1980; NAS 1977a; Schroeder et al. 1987).

5.4.2 Water

Arsenic is widely distributed in surface water, groundwater, and finished drinking water in the United States. Surveys of arsenic concentrations in rivers and lakes indicate that most values are below 10 ppb, although individual samples may range up to 1,000 ppb (NAS 1977b; Page 1981; Smith et al. 1987; Welch et al. 1988). The median arsenic concentration for surface water samples recorded in the STORET database was 3 ppb (EPA 1982c). Arsenic has also been detected in rainwater at average concentrations of 0.2–0.5 ppb and in seawater at an average level of 2 ppb (Welch et al. 1988).

Arsenic levels in groundwater average about 1–2 ppb, except in some western states with volcanic rock and sulfide mineral deposits high in arsenic, where arsenic levels up to 3,400 ppb have been observed (IARC 1980; Page 1981; Robertson 1989; Welch et al. 1988). In western mining areas, groundwater arsenic concentrations up to 48,000 ppb have been reported (Welch et al. 1988).

Surveys of drinking water in the United States have found that more than 99% of public water supplies have arsenic concentrations below the EPA Maximum Contaminant Level (MCL) of 50 ppb (EPA 1984a). In an EPA study of tap water from 3,834 U.S. residences, the average value was 2.4 ppb (EPA 1982c). However, drinking water in polluted areas may have much higher levels; mean arsenic concentration in tapwater from homes near a smelter was 90 ppb (Morse et al. 1979).

Most arsenic in natural waters is a mixture of arsenate and arsenite, with arsenate usually predominating (Braman and Foreback 1973; EPA 1982c, 1984a). Methylated forms have also been detected in both surface and groundwater, at levels ranging from 0.01 to 7.4 ppb (Braman and Foreback 1973; Hood 1985), with most values below 0.3 ppb (Hood 1985).

5.4.3 Soil

Arsenic is found in the earth's crust at an average level of 2 ppm (NAS 1977b). Most natural soils contain low levels of arsenic, but industrial wastes and pesticide applications may increase concentrations. Background arsenic concentrations in soil range from about 1 to 40 ppm, with a mean value of about 5 ppm (Beyer and Cromartie 1987; Eckel and Langley 1988; EPA 1982a; NAS 1977a). Soils overlying arsenic-rich geologic deposits such as sulfide ores may have soil concentrations two orders of magnitude higher (NAS 1977a). Arsenic concentrations up to 27,000 ppm were reported in soils contaminated with mine or smelter wastes (EPA 1982a). Soil on agricultural lands treated with arsenical pesticides may retain substantial amounts of arsenic. One study reported an arsenic concentration of 22 ppm in treated soil compared to 2 ppm for nearby untreated soil (EPA 1982a).

Sediments in aquatic systems often have higher arsenic concentrations than those of the water (Welch et al. 1988). Most sediment arsenic concentrations reported for U.S. rivers, lakes, and streams range from 0.1 to 4,000 ppm, but much higher levels may occur in areas of contamination (Heit et al. 1984; NAS 1977a; Welch et al. 1988).

5.4.4 Other Environmental Media

Arsenic is found in many types of food. The highest levels are detected in seafood, meats, and grains. Typical U.S. dietary levels of arsenic in these foods range from 0.02 ppm in grains and cereals to 0.14 ppm in meat, fish, and poultry (Gartrell et al. 1986), but there is a wide range of values. Shellfish and other marine foods contain the greatest arsenic concentrations (Jelinek and Corneliussen 1977). Mean levels in fish and seafood are usually about 4–5 ppm (Bennett 1986; Schroeder and Balassa 1966), but may be as high as 170 ppm (NAS 1977b).

It is important to bear in mind that much of the arsenic present in fish and shellfish exists in an organic form that is essentially nontoxic. However, some of the arsenic in these foods is in inorganic form. For example, a recent study in the Netherlands reported that inorganic arsenic comprised 0.1–41% of the total arsenic in seafood (Vaessen and van Ooik 1989).

Arsenic is frequently found in plants, often as a result of pesticide treatment (NAS 1977a). Concentrations typically vary from 0.01 to 5 ppm (NAS 1977a). Tobacco levels of arsenic average 1.5 ppm, or about 1.5 µg per cigarette (EPA 1984a). Arsenic has also been detected in several homeopathic medicines at concentrations up to 650 ppm (Kerr and Saryan 1986).

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

For the general population, food is generally the greatest source of arsenic exposure. In the United States, food intake of arsenic has recently been estimated to be about 46 µg/day, with the largest contribution from meat, fish, poultry, grain, and cereal products (Gartrell et al. 1986). Some of this is probably in the form of organic arsenicals (see Section 5.4.4). Drinking water may also be a significant source of arsenic exposure. Estimates of arsenic intake for adults drinking 2 liters of water per day average about 5 µg/d (EPA 1982c), but could be

higher (10–100 μg/d) where levels in water are above average. It is assumed that nearly all arsenic in drinking water is inorganic (EPA 1984a).

Inhalation of arsenic from ambient air is usually a minor exposure route for the general population. For example, the dose to a person who breathes 20 m^3/day of air containing 20–30 ng/m^3 (see Section 5.4.1) would be about 0.4–0.6 μg/d. However, smokers may be exposed to arsenic by inhalation of mainstream smoke. Assuming that 20% of the arsenic in cigarettes is present in smoke, an individual smoking two packs of cigarettes per day would inhale about 12 μg of arsenic (EPA 1984a).

Occupational exposure to arsenic may be significant in several industries, mainly nonferrous smelting, arsenic production, wood preservation, glass manufacturing, and arsenical pesticide production and application. The National Institute for Occupational Safety and Health (NIOSH) estimated that about 55,000 workers were exposed to arsenic in the early 1980s (NOES 1990). The principal exposure pathway is probably inhalation of arsenic adsorbed to particulates, but ingestion and possibly dermal exposure may also be common. However, no information was located on typical exposure levels in the workplace. Since arsenic is no longer produced in the United States (see Section 4.1), and many arsenical pesticide uses have recently been banned (see Chapter 7), it is likely that the number of workers occupationally exposed to arsenic has decreased in recent years.

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

As noted above, workers in a number of industries may have high exposures to arsenic, especially if proper safety procedures are not followed. For members of the general population, above-average exposure to arsenic from drinking water is possible in areas of high natural arsenic levels in groundwater or elevated arsenic levels in drinking water due to industrial discharges, pesticide applications, or leaching from hazardous waste facilities. Individuals living in the vicinity of large smelters and other industrial emitters of arsenic may be exposed to above average arsenic levels both in the air and, as a result of atmospheric deposition, in water and soil.

Smokers and those regularly consuming large amounts of seafood may also be exposed to higher than average levels of arsenic.

5.7 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of arsenic is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of arsenic.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce or eliminate the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

5.7.1 Identification of Data Needs

Physical and Chemical Properties. The chemical and physical properties of the arsenic species of chief toxicological and environmental concern are sufficiently well characterized to allow estimation of the

environmental fates of these compounds. However, more information regarding the K_{ow} and K_{oc} values of the organic arsenicals would help predict the fate of these compounds in the environment.

Production, Import/Export, Use, and Release and Disposal. Arsenic and arsenic trioxide are no longer produced in the United States (U.S. Bureau of Mines 1988, 1990), but substantial quantities are imported (TRI88 1990). It appears that most uses of inorganic pesticides have been discontinued, but in some cases, organic arsenicals may be used instead. Current production and use data for individual arsenical pesticides would help to estimate human exposure to the various arsenic species.

According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The Toxics Release Inventory (TRI), which contains this information for 1988, became available in May of 1990. This database will be updated yearly and should provide a list of industrial production facilities and emissions.

Environmental Fate. The interconversion of the various arsenic species and transport among the environmental media is complex and not all aspects are well-studied. Additional quantitative data on the rates of oxidation, reduction, and biotransformation reactions of arsenic, and how these depend on environmental conditions would be useful in evaluating and predicting the fate and transport of arsenic at hazardous waste sites.

Bioavailability from Environmental Media. Toxicokinetic and toxicity studies establish that arsenic is absorbed following inhalation and oral exposure. The influence of environmental matrix (soil, food) on absorption has not been systematically investigated, and quantitative studies to determine whether absorption is significantly influenced by these media would be valuable. Although absorption from dermal contact is usually considered to be minor, studies to determine if uptake occurs from contact with contaminated soil or water would be helpful, since humans may be exposed by these routes near hazardous waste sites.

Food Chain Bioaccumulation. Bioconcentration factors have been measured for several freshwater and marine species. While some species (mainly marine algae and shellfish) tend to bioconcentrate arsenic (EPA 1980a), it does not appear to be biomagnified through the food chain (Callahan et al. 1979; EPA 1982a, 1983e). Further research on the uptake of arsenic from soil into plants would be valuable in assessing human exposure near waste sites (e.g., through consumption of vegetables from home gardens).

Exposure Levels in Environmental Media. Extensive monitoring data are available for total arsenic in all environmental media. However, most of the data are more than three years old and few studies have monitored individual arsenic species in air, water, or soil. Additional monitoring studies that include complete arsenic speciation data would allow more precise estimation of current exposure levels and possible human health risks.

Exposure Levels in Humans. Arsenic has been detected in human tissues, including blood, urine, hair, nails, and internal organs. Data are available for populations exposed in the workplace and for the general population, but no studies have been published on exposures near waste sites. Biomonitoring studies of residents near waste sites that contain arsenic would be helpful in evaluating the likely human health risks from these sites.

Exposure Registries. No exposure registries for arsenic were located. This compound is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The compound will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to the exposure to this compound.

5.7.2 On-going Studies

Arsenic is included in several monitoring and research programs sponsored by the federal government through various agencies. Arsenic is one of the elements included in the Total Diet Studies conducted by the U.S. Food and Drug Administration. Additional data on current arsenic levels in food will be provided as these studies are updated (Gartrell et al. 1986). The National Contaminant Biomonitoring Program also includes arsenic as one of the contaminants analyzed for in fish and wildlife (Schmitt and Brumbaugh 1990).

As part of the Third National Health and Nutrition Evaluation Survey (NHANES III), the Environmental Health Laboratory Sciences Division of the Center for Environmental Health and Injury Control, Centers for Disease Control, will be analyzing 200 human urine samples for arsenic. The data from this pilot program will give an indication of the frequency of occurrence and background levels of arsenic in the general population and will be compared to historic data from an environmental exposure study in the Tacoma, Washington area (Paschal 1990).

Studies to investigate the interactions and relationships of arsenic species under conditions prevalent in natural aquifers are being conducted by the U.S. Geological Survey (Robertson 1989). The results of these studies may be useful in predicting the behavior of arsenic in the environment.

Remedial investigations and feasibility studies at NPL sites that contain arsenic will also provide further information on environmental concentrations and human exposure levels near waste sites.

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting and/or measuring and monitoring arsenic in environmental media and in biological samples. The intent is not to provide an exhaustive list of analytical methods that could be used to detect and quantify arsenic. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used to detect arsenic in environmental samples are the methods approved by federal organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that refine previously used methods to obtain lower detection limits, and/or to improve accuracy and precision.

6.1 BIOLOGICAL MATERIALS

Atomic absorption spectrophotometry (AAS) is the most common analytical procedure for measuring arsenic in biological materials (Curatola et al. 1978; Foa et al. 1984; Johnson and Farmer 1989; Mushak et al. 1977; Norin and Vahter 1981; Sotera et al. 1988). In AAS analysis, the sample is heated in a flame or in a graphite furnace until the element atomizes. The ground-state atomic vapor absorbs monochromatic radiation from a source and a photoelectric detector measures the intensity of transmitted radiation (APHA 1989b).

Samples may be prepared for AAS in a variety of ways. Most often, the gaseous hydride procedure is employed (Curatola et al. 1978; Foa et al. 1984; Johnson and Farmer 1989; Norin and Vahter 1981). In this procedure, arsenic in the sample is reduced to arsine (AsH_3), a gas which is then trapped and introduced into the flame. This approach measures total inorganic arsenic, but may not detect all organic forms unless a digestion step is included. Digestion or wet-ashing with nitric, sulfuric and/or perchloric acids degrades the organic arsenic species to inorganic arsenic so that recovery of total arsenic from biological materials can be achieved (Maher 1989; Mushak et al. 1977; Versieck et al. 1983).

The arsenic concentration in biological fluids and tissues may also be determined by neutron activation analysis (NAA) (Landsberger and Simsons 1987; Versieck et al. 1983). In this approach, the sample is irradiated with a source of neutrons which converts a portion of the arsenic atoms to radioactive isotopes which can be quantified after separation from radioisotopes of other chemicals. X-ray fluorescence is also capable of measuring arsenic in biological materials (Bloch and Shapiro 1986; Clyne et al. 1989; Nielson and Sanders 1983) and environmental samples (see Section 6.2). This method has the advantage that no sample digestion or separation steps are required.

Speciation of arsenic (i.e., analysis of individual forms rather than total) is usually accomplished by employing separation procedures prior to introduction of the sample material into a detection system. Various types of chromatography or chelation-extraction techniques are most commonly used (Dix et al. 1987; Foa et al. 1984; Johnson and Farmer 1989; Mushak et al. 1977; Norin et al. 1987). Another approach involves selective reduction of arsenate and arsenite (permitting quantification of individual inorganic arsenic species), and selective distillation of methyl arsines to quantify MMA and DMA (Andreae 1977; Braman et al. 1977; Crecelius 1978).

Table 6-1 summarizes a variety of methods for measuring total arsenic and individual arsenic species in biological materials. None of these methods have been standardized by EPA or other federal agencies. Detection limits in blood and urine are about 0.1–1 ppb for most techniques, while limits for hair and tissues are usually somewhat higher.

TABLE 6-1. Analytical Methods for Determining Arsenic in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Methods for total arsenic:					
Blood	Digest with nitric acid and hydrogen peroxide, dry ash with magnesium oxide/magnesium nitrate, reduce arsenic to arsine with sodium borohydride	AAS/hydride generation	0.5 µg/L	95–102	Foa et al. 1984
Blood	Wet ash with nitric/perchloric acids, reduce with sodium borohydride	AAS/hydride generation	0.1 µg/L[a]	95–105	Valentine et al. 1979
Serum	Irradiate, digest with nitric/perchloric/sulfuric acids, extract with toluene	NAA	0.088 ng/mL[a]	94–98	Versieck et al. 1983
Urine	Irradiate epithermally	NAA	40–100 ng/g	93–109	Landsberger and Simsons 1987
Urine	Digest with nitric and perchloric acid. Reduce with stannous chloride, generate arsine by addition of zinc	Spectrophotometric (SDDC)	0.5 µg/sample	90–110	Pinto et al. 1976
Urine	Dry ash with magnesium oxide/magnesium nitrate, reduce arsenic to arsine with sodium borohydride	AAS/hydride generation	0.5 µg/L	95–102	Foa et al. 1984
Urine	Dry, irradiate with x-rays	XRF	0.2 µg/L[a]	92–108	Clyne et al. 1989

TABLE 6-1 (Continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Hair	Ash with nitric/sulfuric acids and hydrogen peroxide, reduce arsenic to arsine with sodium borohydride	AAS/hydride generation	0.06 µg/g	93	Curatola et al. 1978
Hair	Wet ash with nitric/perchloric acids, reduce with sodium borohydride	AAS/hydride generation	0.01 µg/g[a]	95–105	Valentine et al. 1979
Soft tissues	Digest with nitric/sulfuric acids, complex with DDDC in potassium iodide, extract with chloroform	AAS/graphite furnace	0.2 ppm	79.8	Mushak et al. 1977
Nails	Wash with acetone, soap, dilute acid, ammonium hydroxide; digest in concentrated nitric and sulfuric acids, than add hydrogen peroxide	AAS/hydride generation	1.5 µg/g	No data	Agahian et al. 1990
Methods for arsenic speciation:					
Urine	Separate As^{+3}, As^{+5}, MMA, DMA on anion/cation exchange resin column by elution with trichloroacetic acid, reduce each species to arsine with sodium borohydride	IEC/AAS/hydride generation	0.5 µg/L	93–106	Johnson and Farmer 1989
Urine	Reduce inorganic arsenic, MMA and DMA to arsine with sodium borohydride	AAS/hydride generation	0.08 µg/L	97–104	Norin and Vahter 1981

TABLE 6-1 (Continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Urine	Reduce As^{+3}, As^{+5}, MMA, and DMA to arsine and methyl arsines; collect in cold trap, separate by slow warming	Atomic emission	1 ng	No data	Braman et al. 1977
Urine	Extract with chloroform, then methanol; elute on column with chloroform/methanol, then elute on cation exchange column with ammonium hydroxide	AAS/hydride generation/TLC/ HRMS	0.34 mg/ sample[a]	No data	Tam et al. 1982
Blood/tissue	Digest with hydrochloric acid, complex with TGM, extract with cyclohexane, elute on capillary column	GLC/ECD	0.1 mg/mL	No data	Dix et al. 1987

[a]Lowest reported concentration

AAS = atomic absorption spectrophotometry; DDDC = diethylammonium diethyldithiocarbamate; DMA = dimethylarsinate; ECD = electron capture detector; GLC = gas-liquid chromatography; HRMS = high resolution mass spectrometry; IEC = ion exchange chromatography; MMA = monomethylarsonate; NAA = neutron activation analysis; SDDC = silver diethyldithiocarbamate; TGM = thioglycolic acid methylester; TLC = thin layer chromatography; XRF = X-ray fluorescence

6.2 ENVIRONMENTAL SAMPLES

Arsenic in environmental samples is also measured most often by AAS techniques, with samples prepared by digestion with nitric, sulfuric and/or perchloric acids (Dabeka and Lacroix 1987; EPA 1983a, 1983b; Hershey et al. 1988). A spectrophotometric technique, in which a soluble red complex of arsine and silver diethyldithiocarbamate (SDDC) is formed, inductively-coupled plasma atomic emission spectroscopy (ICP) (APHA 1977; EPA 1982b, 1983c), and X-ray fluorescence (Khan et al. 1989; Nielson and Sanders 1983) are also employed.

Since arsenic in air is usually associated with particulate matter, standard methods involve collection of air samples on glass fiber or membrane filters, acid extraction of the filters, arsine generation and analysis by SDDC spectrophotometry or AAS (APHA 1977; NIOSH 1984).

Four methods standardized by EPA (1982b, 1983a, 1983b, 1983c, 1986c, 1986d) are generally used for measuring total arsenic in water, wastewater, soil, or sediments. Similar methods are recommended by APHA for water using AAS/hydride generation (APHA 1989c), AAS/graphite furnace technique (APHA 1989b), ICP (APHA 1989d) or SDDC spectrophotometry (APHA 1989a). The AAS/hydride generation method is generally preferred because it is more resistant to matrix and chemical interferences than the other methods (APHA 1989a). Techniques to compensate for these interferences have been described by EPA (1982b).

Analysis for arsenic in foods is also most frequently accomplished by AAS techniques (Arenas et al. 1988; Dabeka and Lacroix 1987; Hershey et al. 1988; Tam and Lacroix 1982). Hydride generation is the sample preparation method most often employed (Arenas et al. 1988; Hershey et al. 1988), but interferences must be evaluated and minimized.

Speciation of inorganic arsenic in environmental samples is usually accomplished by chelation-extraction or elution of As+3 and then reduction of As+5 with subsequent similar treatment (Butler 1988; Mok et al. 1988; Rabano et al. 1989). Methods are also available for quantifying organic arsenicals in environmental media, including arsenobetaine in fish (Beauchemin et al. 1988; Cannon et al. 1983) and other organic forms of arsenic in water and soil (Andreae 1977; Braman et al. 1977; Comber and Howard 1989; Crecelius 1978; Odanaka et al. 1983).

A summary of selected methods for analysis of total arsenic and individual inorganic and organic arsenic species in environmental samples is presented in Table 6-2.

6.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of arsenic is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of arsenic.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce or eliminate the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

TABLE 6-2. Analytical Methods for Determining Arsenic in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Methods for total arsenic:					
Air	Collect samples on membrane or glass fiber filters, digest with hot hydrochloric acid, reduce to arsine by zinc in acid solution	Arsine/SDDC spectrophotometric	0.1 $\mu g/m^3$	86–103	APHA 1977
Air	Collect sample on cellulose ester membrane filter, digest with hot nitric acid, sulfuric acid, and perchloric acid.	AAS/flame arsine generation	0.25 $\mu g/m^3$	No data	NIOSH 1987
Water/wastewater	Digest with nitric acid	ICP-AES	53 µg/L	86–105	EPA 1982b
Water/soil/ solid waste	Digest with nitric acid and hydrogen peroxide, spike with nickel nitrate	AAS/furnace technique	1 µg/L	85–106	EPA 1983a, 1986c
Water/soil/ solid waste	Digest with nitric/sulfuric acid; reduce arsenic to trivalent form with tin chloride, reduce to arsine with zinc in acid solution	AAS/gaseous hydride	2 µg/L	85–94	EPA 1983b, 1986d
Water	Reduce arsenic to arsine in acid solution	Spectrophotometric arsine/SDDC	10 µg/L	100	EPA 1983c
Water	Digest with acid, reduce arsenic to arsine with sodium borohydride in acid solution	AAS/gaseous hydride	2 µg/L	87.3–99.8	APHA 1989c

TABLE 6-2 (Continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Food	Digest with nitric acid, dry ash with magnesium oxide, reduce arsenic with ascorbic acid, precipitate with APDC in presence of nickel carrier	AAS/graphite furnace	10 ng	86–107	Dabeka and Lacroix 1987
Soil	No preparation required	XRF (backscatter)	4 mg/kg	No data	Nielson and Sanders 1983
Food	Digest with nitric/sulfuric/perchloric acids, reduce arsenic with potassium iodide and reduce to arsine with sodium borohydride	AAS/hydride generation	0.1 µg/g	98–110	Hershey et al. 1988
Methods for speciation of inorganic arsenic:					
Air	Collect on polytetrafluoroethylene filter in high volume dichotomous virtual impactor, desorb with hydrochloric acid in presence of ethanol, reduce As^{+3} to arsine with zinc in acid, then reduce to As^{+5} to arsine with sodium tetrahydrodiborate	AAS/hydride generation	1 ng/m^3	95 ±7 (As^{+3}) 100 ±8 (As^{+5})	Rabano et al. 1989
Water	Ultrasonicate, elute with orthophosphoric acid for As^{+3}, reduce As^{+5} to As^{+3} with sulfur dioxide for total As	IEC/amperometric detector	0.012 µM (0.9 µg/L)	95	Butler 1988

TABLE 6-2 (Continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water/soil	Complex As^{+5} with ammonium molybdate, extract with isoamyl alcohol to separate from As^{+3}	AAS	No data	No data	Brown and Button 1979
Water	Extract As^{+3} with APDC into chloroform, back extract with nitric acid; reduce As^{+5} to As^{+3} with thiosulfate and extract	NAA	0.01 ppb	No data	Braman et al. 1977
Water	Selectively reduce As^{+3} and As^{+5} to arsine with sodium borohydride	Atomic emission	1 ng/sample (about 0.01–0.02 ppb)	90–110	Beauchemin et al. 1988
Methods for speciation of organic arsenic:					
Food (fish)	Extract with acetone, extract arsenobetaine with methanol/chloroform, digest with nitric acid/magnesium nitrate	HPLC/ICP-MS	300 pg	101 ±4	Comber and Howard 1989
Water	Reduce inorganic arsenic, MMA and DMA to arsines with sodium tetrahydroborate, control pH to separate As^{+3}, As^{+5}	AAS/hydride generation	0.019–0.061 ng	No data	Andreae 1977
Water	Reduce to arsines, collect in cold trap, separate by slow warming	AAS	2 ng/L	91–109	

TABLE 6-2 (Continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water/Soil	Extract soil with sodium bicarbonate, reduce inorganic arsenic, MMA and DMA to hydrides with sodium borohydride, cold trap arsines in n-heptane	HG-HCT/ GC-MID	0.2-0.4 ng/mL	97-102	Odanaka et al. 1983

AAS = atomic absorption spectrophotometry; APDC = ammonium pyrrolidine dithiocarbamate; DMA = dimethylarsinate; GC-MID = gas chromatography-multiple ion detection; HG-HCT = hydride generation-heptane cold trap; HPLC = high performance liquid chromatography; ICP-AES = inductively coupled plasma-atomic emission spectroscopy; ICP-MS = inductively coupled plasma-mass spectrometry; IEC = ion-exclusion chromatography; MMA = monomethylarsonate; NAA = neutron activation analysis; SDDC = silver diethyldithiocarbamate; XRF = X-ray fluorescence

6.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. The most useful biomarkers of exposure to arsenic are levels of arsenic in urine, hair, or nails. Existing methods are sufficiently sensitive to measure background levels of arsenic in these tissues for average persons, and to detect increases as a result of above-average exposure (Agahian et al. 1990; Curatola et al. 1978; Clyne et al. 1989; Foa et al. 1984; Landsberger and Simsons 1987; Mushak et al. 1977; Pinto et al. 1976; Valentine et al. 1979; Versieck et al. 1983). The precision and accuracy of these methods are documented. Methods are also available that can distinguish nontoxic forms of arsenic (arsenobetaine) from inorganic and organic derivatives that are of health concern (Braman et al. 1977; Dix et al. 1987; Johnson and Farmer 1989; Norin and Vahter 1981; Tam et al. 1982). Further efforts to improve accuracy and reduce interferences would be valuable, but are not essential.

Arsenic is believed to act by inhibition of numerous cell enzymes and/or by interfering with phosphate metabolism, and effects on several enzyme systems have been characterized in animals and in vitro. However, these effects are not specific to arsenic, and most can only be measured in tissue extracts. Efforts to identify an arsenic-specific enzymic or metabolic effect would be valuable, particularly if the effect could be measured using non-invasive techniques, and if the effect were specifically linked to the dermal, neurological, or hematological injuries that are characteristic of arsenic toxicity.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Arsenic is ubiquitous in the environment. It is found in air, water, soil, sediments, and food in several inorganic and organic forms. Analytical methods exist for the analysis of arsenic species in all of these environmental media, and these methods have the sensitivity to measure background levels and to detect elevated concentrations due to emissions from sources such as smelters, chemical plants, or hazardous waste sites (APHA 1977, 1989c; EPA 1982b, 1983a, 1983b, 1983c, 1986c, 1986d). However, further research to reduce chemical and matrix interferences may improve the speed and accuracy of the analyses.

6.3.2 On-going Studies

Methods to reduce interelement interferences and to investigate applications of different capillary columns for separation of various arsenic species are being pursued (Dix et al. 1987; Hershey et al. 1988).

7. REGULATIONS AND ADVISORIES

Because of its potential to cause adverse health effects in exposed people, a number of regulations and guidelines have been established for various inorganic and organic forms of arsenic by international, federal, and state agencies. These values are summarized in Table 7-1.

ATSDR has derived a chronic oral MRL of 0.0003 mg As/kg/day for inorganic arsenic. This MRL is based on a NOAEL of 0.0008 mg As/kg/day observed in a large Taiwanese population exposed to arsenic mainly via drinking water (Tseng 1977; Tseng et al. 1968). An uncertainty factor of 3 was used to account for the fact that the population was relatively young, decreasing the ability to detect any possible effects.

EPA has also derived chronic and subchronic oral Reference Doses (RfDs) of $3x10^{-4}$ mg/kg/day for inorganic arsenic, based on the NOAEL of $8x10^{-4}$ mg/kg/day in humans chronically exposed to arsenic (IRIS 1992; Tseng 1977). The critical effects were keratoses and hyperpigmentation of the skin with possible vascular complications. EPA places medium confidence in the chronic RfD.

TABLE 7-1. Regulations and Guidelines Applicable to Arsenic

Agency	Description	Information	References
INTERNATIONAL			
IARC	*Carcinogenic classification* (Arsenic and arsenic compounds)	Group 1[a]	IARC 1987
WHO	Guideline value for drinking water	0.05 mg/L	WHO 1984a
WHO	Tolerable daily intake for inorganic arsenic	2 μg/kg body weight	Norman et al. 1988
NATIONAL			
Regulations:			
a. Air:			
EPA OAQPS	Hazardous Air Pollutant Inorganic Arsenic	Yes	40 CFR 61
	NESHAP for inorganic arsenic emissions from copper smelters, glass manufacturing plants, and arsenic plants	Yes	EPA 1986f (40 CFR 61)
OSHA	PEL TWA		OSHA 1989
	Organic compounds, as As	500 μg/m^3	(29 CFR
	Inorganic compounds, as As	10 μg/m^3	1910.1000,
	Action level	5 μg/m^3	1910.1018)
b. Water:			
EPA ODW	MCL	0.05 mg/L	40 CFR 141.11
EPA OWRS	General permits under NPDES	Yes	40 CFR 122
	General Pretreatment Regulations for existing and new sources of pollution	Yes	40 CFR 403
c. Food:			
FDA	Permissible concentration in bottled water	0.05 mg/L	21 CFR 103.35
	Tolerances for residues of new animal drugs in food (total residues of combined arsenic, as As)	0.5-2 ppm	21 CFR 556.60
	Diluent in color additive mixtures for food use exempt from certification	1 ppm	21 CFR 73.40, 73.50
d. Other:			
EPA OERR	Reportable quantity		EPA 1989d (40
	Arsenic	1 lb	CFR 302.4)
	Arsenic acid	1 lb	
	Arsenic disulfide	1 lb	
	Arsenic pentoxide	1 lb	
	Arsenic trichloride	1 lb	
	Arsenic trioxide	1 lb	

TABLE 7-1 (Continued)

Agency	Description	Information	References
	Arsenic trisulfide	1 lb	
	Cacodylic acid	1 lb	
	Calcium arsenate	1 lb	
	Calcium arsenite	1 lb	
	Cupric acetoarsenic	1 lb	
	Potassium arsenate	1 lb	
	Potassium arsenite	1 lb	
	Lead arsenate	1 lb	
	Sodium arsenate	1 lb	
	Sodium arsenite	1 lb	
	Extremely Hazardous Substance TPQ	1 lb	EPA 1987b (40 CFR 355)
	Arsenic pentoxide	100/10,000 lb	
	Arsenous oxide	100/10,000 lb	
	Arsenous trichloride	500 lb	
	Calcium arsenate	500/10,000 lb	
	Potassium arsenite	500/10,000 lb	
	Sodium arsenate	1,000/10,000 lb	
	Sodium arsenite	500/10,000 lb	
EPA OPP	Notice of Intent to Cancel Registration of Pesticide Products Containing Inorganic Arsenic for non-Wood Preservative Uses	Yes	EPA 1988a
	Cancellation of Registration of Calcium Arsenate and Lead Arsenate	Yes	EPA 1990c
	Restricted Use Pesticide Inorganic Arsenicals for Wood Preservative Uses	Yes	EPA 1986c
	PEL for arsenic in arsenical pressure treatment plants (8 hr average)	10 $\mu g/m^3$	EPA 1986e
	Tolerances for residues on agricultural commodities	0.35-3.5 ppm	40 CFR 180
	Cacodylic acid		
	Calcium arsenate		
	Copper arsenate		
	Lead arsenate		
	Magnesium arsenate		
	Methanearsonic acid		
	Sodium arsenate		
	Sodium arsenite		
	Revocation of Tolerances (proposed)	Yes	EPA 1990a
	Calcium arsenate		
	Lead arsenate		
EPA OSW	Hazardous Waste Constituent (Appendix VIII)	Yes	EPA 1980d (40 CFR 261)
	Arsenic and compounds (not otherwise specified)		
	Arsenic acid		
	Arsenic pentoxide		
	Arsenic trioxide		

TABLE 7-1 (Continued)

Agency	Description	Information	References
	Groundwater Monitoring List (Appendix IX) Arsenic (total)	Yes	EPA 1987c (40 CFR 264)
	Land Disposal Restrictions	Yes	EPA 1987d, 1988b, 1990b (40 CFR 268)
EPA OTS	Toxic Chemical Release Reporting Rule Arsenic Arsenic compounds	Yes	EPA 1988a (40 CFR 372)
Guidelines:			
a. Air:			
ACGIH	TLV TWA		ACGIH 1990
	Arsenic and soluble compounds, as As	0.2 mg/m^3	
	Arsenic trioxide production	Suspected human carcinogen	
NIOSH	Recommended exposure limit for occupation exposure		NIOSH 1990
	Ceiling (15 minute)	2 $\mu g/m^3$	
	Potential occupational carcinogen	Yes	
b. Water:			
EPA ODW	MCLG (proposed)	0.05 mg/L	EPA 1985c
EPA OWRS	Ambient Water Quality Criteria		EPA 1980a
	Ingesting water and organisms:	$2.2x10^{-6}$ mg/L[b]	
	Ingesting organisms only:	$1.75x10^{-5}$ mg/L[b]	
c. Other:			
EPA	RfD (oral)	$3x10^{-4}$ mg/kg/day[c]	IRIS 1992
	Carcinogenic Classification	Group A[d]	IRIS 1992
	Cancer slope factor (q_1*)		IRIS 1992
	q_1* (oral)	1.75 $(mg/kg/day)^{-1}$	
	q_1* (inhalation)	15 $(mg/kg/day)^{-1}$	
NTP	Carcinogen Classification	Known carcinogen	NTP 1989a
STATE			
Regulations and Guidelines:			
a. Air: Arsenic and compounds	Acceptable ambient air concentrations		NATICH 1989
Connecticut		$5.0x10^{-2}$ $\mu g/m^3$ (8 hr)	
Kansas (Kansas City)		$2.33x10^{-4}$ $\mu g/m^3$ (annual)	
Montana		$7.0x10^{-2}$ $\mu g/m^3$ (annual) $3.9x10^{-1}$ $\mu g/m^3$ (24 hr)	

TABLE 7-1 (Continued)

Agency	Description	Information	References
STATE (Continued)			
Nevada		5.0×10^{-3} mg/m^3 (8 hr)	
New York		6.7×10^{-1} µg/m^3 (1 yr)	
North Carolina		2.3×10^{-7} mg/m^3 (annual)	
Pennsylvania (Philadelphia)		2.4×10^{-2} µg/m^3 (annual)	
Rhode Island		2.0×10^{-4} µg/m^3 (annual)	
South Carolina		1.0 µg/m^3 (24 hr)	
Vermont		2.3×10^{-4} µg/m^3 (annual)	
Virginia		3.3 µg/m^3 (24 hr)	
Arsenic chloride			
Arsenic sulfide			
North Carolina		2.3×10^{-7} mg/m^3 (annual)	
Arsenic pentoxide			
North Carolina		2.3×10^{-7} mg/m^3 (annual)	
South Carolina		1 µg/m^3 (24 hr)	
Arsenic trioxide			
North Carolina		2.3×10^{-7} mg/m^3 (annual)	
Virginia		3.0 µg/m^3 (24 hr)	
b. Water:	Drinking water quality standards		FSTRAC 1990
Alabama		50 µg/L	
Arizona		50 µg/L	
Maine		30 µg/L	
Massachusetts		50 µg/L	
Minnesota		50 µg/L	
Rhode Island		50 µg/L	
Vermont		50 µg/L	

[a]Group 1 = Carcinogenic to humans; classification applies to the group of compounds as a whole but not necessarily to each individual compound in the group.
[b]For an incremental increased lifetime cancer risk of 10^{-6}.
[d]Group A = carcinogenic to humans

ACGIH = American Conference of Governmental Industrial Hygienists; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; IARC = International Agency for Research on Cancer; IDLH = Immediately Dangerous to Life or Health Level; MCL = Maximum Contaminant Level; MCLG = Maximum Contaminant Level Goal; NESHAP = National Emission Standards for Hazardous Air Pollutants; NIOSH = National Institute for Occupational Safety and Health; NPDES = National Pollutant Discharge Elimination System; NTP = National Toxicology Program; OAQPS = Office of Air Quality Planning and Standards; ODW = Office of Drinking Water; OERR = Office of Emergency and Remedial Response; OPP = Office of Pesticide Products; OSHA = Occupational Safety and Health Administration; OSW = Office of Solid Waste; OTS = Office of Toxic Substances; OWRS = Office of Water Regulations and Standards; PEL = Permissible Exposure Limit; RfD = Reference Dose; STEL = Short Term Exposure Limit; TLV = Threshold Limit Value; TPQ = Threshold Planning Quantity; TWA = Time-Weighted Average; WHO = World Health Organization

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9. GLOSSARY

Acute Exposure -- Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption Coefficient (K_{oc}) -- The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd) -- The amount of a chemical adsorbed by a sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Bioconcentration Factor (BCF) -- The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Cancer Effect Level (CEL) -- The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen -- A chemical capable of inducing cancer.

Ceiling Value -- A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure -- Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Developmental Toxicity -- The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Embryotoxicity and Fetotoxicity -- Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurred. The terms, as used here, include malformations and variations, altered growth, and in utero death.

EPA Health Advisory -- An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH) -- The maximum environmental concentration of a contaminant from which one could escape within 30 min without any escape-impairing symptoms or irreversible health effects.

Intermediate Exposure -- Exposure to a chemical for a duration of 15-364 days, as specified in the Toxicological Profiles.

Immunologic Toxicity -- The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

In Vitro -- Isolated from the living organism and artificially maintained, as in a test tube.

9. GLOSSARY

In Vivo -- Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO}) -- The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50}) -- A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{LO}) -- The lowest dose of a chemical introduced by a route other than inhalation that is expected to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50}) -- The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50}) -- A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL) -- The lowest dose of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Malformations -- Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level -- An estimate of daily human exposure to a dose of a chemical that is likely to be without an appreciable risk of adverse noncancerous effects over a specified duration of exposure.

Mutagen -- A substance that causes mutations. A mutation is a change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

Neurotoxicity -- The occurrence of adverse effects on the nervous system following exposure to chemical.

No-Observed-Adverse-Effect Level (NOAEL) -- The dose of chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow}) -- The equilibrium ratio of the concentrations of a chemical in n-octanol and water, in dilute solution.

Permissible Exposure Limit (PEL) -- An allowable exposure level in workplace air averaged over an 8-hour shift.

q_1^* -- The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1^* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually µg/L for water, mg/kg/day for food, and µg/m^3 for air).

Reference Dose (RfD) -- An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the NOAEL (from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an

additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ) -- The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity -- The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Short-Term Exposure Limit (STEL) -- The maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily TLV-TWA may not be exceeded.

Target Organ Toxicity -- This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen -- A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV) -- A concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a TWA, as a STEL, or as a CL.

Time-Weighted Average (TWA) -- An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose (TD_{50}) -- A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Uncertainty Factor (UF) -- A factor used in operationally deriving the RfD from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

APPENDIX A

USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in nontechnical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or substance release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the substance.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-1, 2-2, and 2-3) and figures (2-1 and 2-2) are used to summarize health effects by duration of exposure and endpoint and to illustrate graphically levels of exposure associated with those effects. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse-Effect Levels (NOAELs). Lowest-Observed- Adverse-Effect Levels (LOAELs) for Less Serious and Serious health effects, or Cancer Effect Levels (CELs). In addition, these tables and figures illustrate differences in response by species, Minimal Risk Levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper-bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. The LSE tables and figures can be used for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text.

The legends presented below demonstrate the application of these tables and figures. A representative example of LSE Table 2-1 and Figure 2-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 2-1

(1). Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 2-1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-1) and oral (LSE Figure 2-2) routes.

(2). Exposure Duration Three exposure periods: acute (14 days or less); intermediate (15 to 364 days); and chronic (365 days or more) are presented within each route of exposure. In this example, an inhalation study of intermediate duration exposure is reported.

(3). Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table.

(4). Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to define a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in Figure 2-1).

(5). Species The test species, whether animal or human, are identified in this column.

(6). Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to [substance x] via inhalation for 13 weeks, 5 days per week, for 6 hours per day.

(7). System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated in this study.

(8). NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9). LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest exposure level used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The "Less Serious" respiratory effect reported in key number 18 (hyperplasia) occurred at a LOAEL of 10 ppm.

(10). Reference The complete reference citation is given in Chapter 8 of the profile.

(11). CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiological studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses which did not cause a measurable increase in cancer.

(12). Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

APPENDIX A

LEGEND

See LSE Figure 2-1

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure levels for particular exposure duration.

(13). Exposure Duration The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.

(14). Health Effect These are the categories of health effects for which reliable quantitative data exist. The same health effects appear in the LSE table.

(15). Levels of Exposure Exposure levels for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure levels are reported on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16). NOAEL In this example, 18r NOAEL is the critical end point for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates a NOAEL for the test species (rat). The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17). CEL Key number 38r is one of three studies for which Cancer Effect Levels (CELs) were derived. The diamond symbol refers to a CEL for the test species (rat). The number 38 corresponds to the entry in the LSE table.

(18). Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1^*).

(19). Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

SAMPLE

1 → TABLE 2-1. Levels of Significant Exposure to [Chemical x] - Inhalation

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE							
3 → Systemic	5	6	7	8	9		10
4 → 18	Rat	13 wk 5d/wk 6hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
Cancer					11		
38	Rat	18 mo 5d/wk 7hr/d			20 (CEL, multiple organs)		Wong et al. 1982
39	Rat	89-104 wk 5d/wk 6hr/d			10 (CEL, lung tumors, nasal tumors)		NTP 1982
40	Mouse	79-103 wk 5d/wk 6hr/d			10 (CEL, lung tumors, hemangiosarcomas)		NTP 1982

[a] The number corresponds to entries in Figure 2-1.

12 → [b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5×10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

CEL = cancer effect level; d = day(s); hr = hour(s); LOAEL = lowest-observed-adverse-effect level; mo = month(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

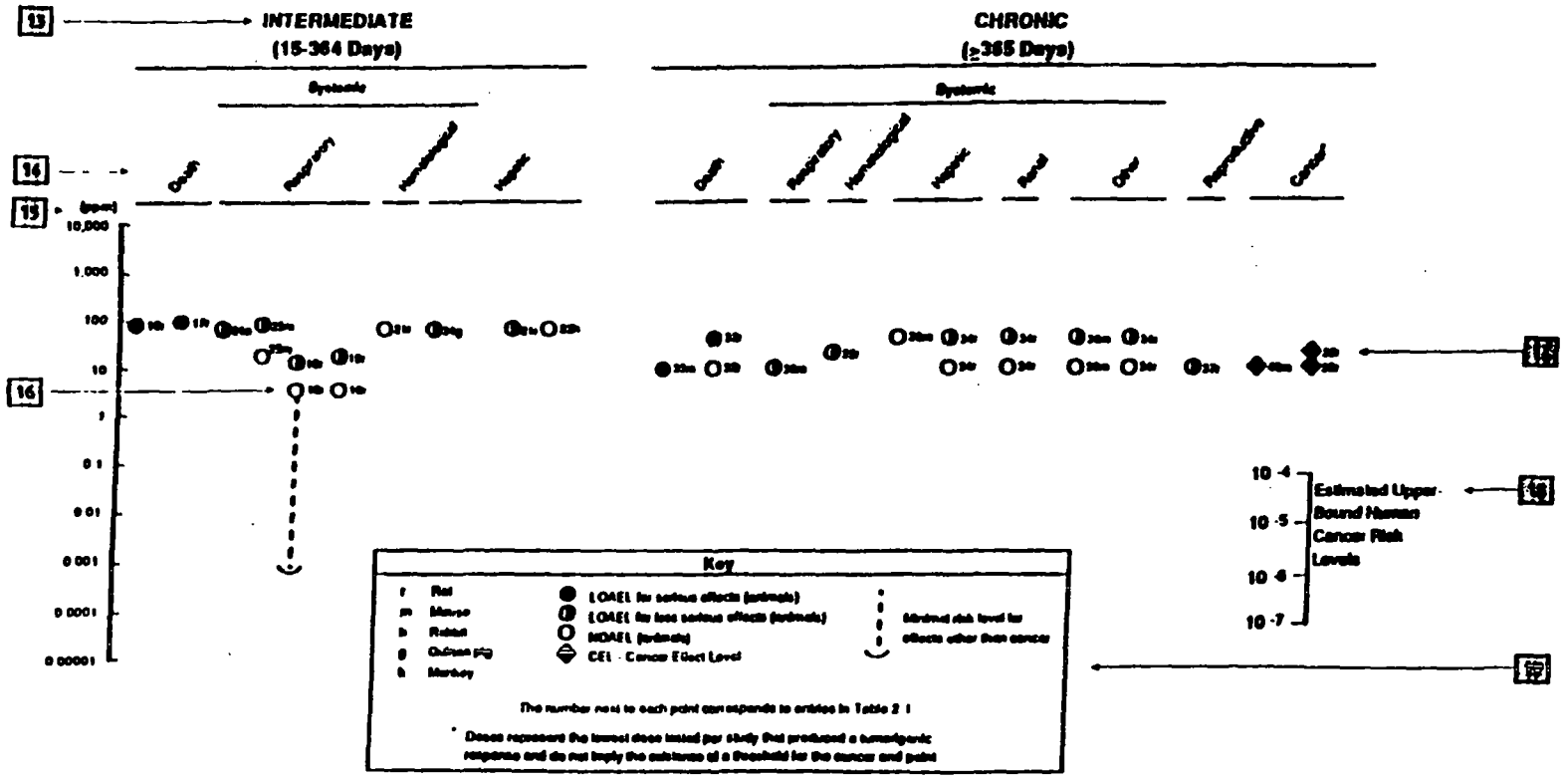

FIGURE 2-1. Levels of Significant Exposure to [Chemical X]-Inhalation

APPENDIX A

Chapter 2 (Section 2.4)

Relevance to Public Health

The Relevance to Public Health section provides a health effects summary based on evaluations of existing toxicological, epidemiological, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions.

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The section discusses health effects by end point. Human data are presented first, then animal data. Both are organized by route of exposure (inhalation, oral, and dermal) and by duration (acute, intermediate, and chronic). In vitro data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this section. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. MRLs for noncancer end points if derived, and the end points from which they were derived are indicated and discussed in the appropriate section(s).

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Identification of Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information was available, MRLs were derived. MRLs are specific for route (inhalation or oral) and duration (acute, intermediate, or chronic) of exposure. Ideally, MRLs can be derived from all six exposure scenarios (e.g., Inhalation - acute, -intermediate, -chronic; Oral - acute, -intermediate, - chronic). These MRLs are not meant to support regulatory action, but to aquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a substance emission, given the concentration of a contaminant in air or the estimated daily dose received via food or water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicological information on which the number is based. Section 2.4, "Relevance to Public Health," contains basic information known about the substance. Other sections such as 2.6, "Interactions with Other Chemicals" and 2.7, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology used by the Environmental Protection Agency (EPA) (Barnes and Dourson, 1988; EPA 1989a) to derive reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential effects (e.g., systemic, neurological, and developmental). In order to compare NOAELs and LOAELs for specific end points, all inhalation exposure levels are adjusted for 24hr exposures and all intermittent exposures for inhalation and oral routes of intermediate and chronic duration are adjusted for continous exposure (i.e., 7 days/week). If the information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. The NOAEL is the most suitable end point for deriving an MRL. When a NOAEL is not available, a Less Serious LOAEL can be used to derive an MRL, and an uncertainty factor (UF) of 10 is employed. MRLs are not derived from Serious LOAELs. Additional uncertainty factors of 10 each are used for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the adjusted inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

APPENDIX B

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADME	Absorption, Distribution, Metabolism, and Excretion
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BSC	Board of Scientific Counselors
C	Centigrade
CDC	Centers for Disease Control
CEL	Cancer Effect Level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
CLP	Contract Laboratory Program
cm	centimeter
CNS	central nervous system
d	day
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DMA	Dimethylarsinic acid
DOL	Department of Labor
ECG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
EKG	see ECG
F	Fahrenheit
F_1	first filial generation
FAO	Food and Agricultural Organization of the United Nations
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
fpm	feet per minute
ft	foot
FR	Federal Register
g	gram
GC	gas chromatography
gen	generation
HPLC	high-performance liquid chromatography
hr	hour
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient

L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
mg	milligram
min	minute
mL	milliliter
mm	millimeter
MMA	Monomethylarsonic acid
mmHg	millimeters of mercury
mmol	millimole
mo	month
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
ng	nanogram
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPL	National Priorities List
NRC	National Research Council
NTIS	National Technical Information Service
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
RfD	Reference Dose
ROX	Roxarsone (3-nitro-4-hydroxyphenylarsonic acid)
RTECS	Registry of Toxic Effects of Chemical Substances
sec	second

SCE	sister chromatid exchange
SIC	Standard Industrial Classification
SMR	standard mortality ratio
STEL	short term exposure limit
STORET	STORAGE and RETRIEVAL
TLV	threshold limit value
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
yr	year
WHO	World Health Organization
wk	week
>	greater than
$\geq$	greater than or equal to
=	equal to
<	less than
$\leq$	less than or equal to
%	percent
α	alpha
β	beta
δ	delta
γ	gamma
μm	micron
μg	microgram

APPENDIX C

PEER REVIEW

A peer review panel was assembled for arsenic. The panel consisted of the following members: Dr. Eric Crecelius, Senior Research Scientist, Battelle Pacific Northwest, Sequim, WA; Dr. Philip Enterline, Emeritus Professor of Biostatistics, University of Pittsburgh, Pittsburgh, PA; Dr. Ingeborg Harding-Barlow, Private Consultant, Palo Alto, CA. These experts collectively have knowledge of arsenic's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(i)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

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